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Special Issue

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*Warter, P. J.: Prednisolone-hydroxyzine combination in rheumatoid arthritis, J. M. Soc. New Jersey 54:7, 1957.

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1. Grossman, A. J., Batterman, R. C., and Leifer, P.: Comparative Testing of Daytime Sedatives and Hypnotic Medications, Fed. Proc. 17:373 (March) 1958.

2. Batterman, R. C., Grossman, A. J., Leifer, P., and Mouratoff, G. J.: Clin Re-evaluation of Daytime Sedatives, Postgrad. Med. 26:502-509 (October) 1

Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• CONGENITAL ABSENCE OF APPENDIX

Q. An 18 year old boy had clinical symptoms of appendicitis. The white blood cell count was 10,970, with 80 per cent polymorphonuclear leukocytes. Careful exploration of the right iliac fossa failed to reveal an appendix. The abdomen was closed and recovery was uneventful.

This patient had had no previous abdominal surgery. Is it possible for the appendix to be congenitally absent?

M.D.—New York

A. Congenital absence of the appendix is very rare indeed. For further information, see W. H. Hollinshead, "Anatomy for Surgeons," New York, Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, 1956, vol. 2, p. 521.

• TRANSPLANTED VACCINIA

Q. A 71 year old woman was vaccinated for smallpox. The vaccination took moderately well, but the woman transplanted the vaccinia while scratching in her sleep. One week later, vaccinia was observed on the lower part of her abdomen. Three months later, she still had single eruptions at various locations. What can be done to stop spread of the vaccinia?

M.D.—Manitoba

A. Transplanted vaccinia of this type will gradually disappear in most patients. If facilities are available, it would be worthwhile to examine this patient for hypogammaglobulinemia. Whether or not this is done, gamma-globulin might be given empirically. If possible, the gamma-globulin should be hyperimmune (from a previously vaccinated donor). Supplementary treatment with an antiseptic detergent such as pHisoHex® to prevent secondary infection, and perhaps a locally applied antibiotic cream or lotion might be worthwhile. However, such measures will not relieve the basic cause. Oral administration of antibiotic agents or steroids or both probably would be undesirable.

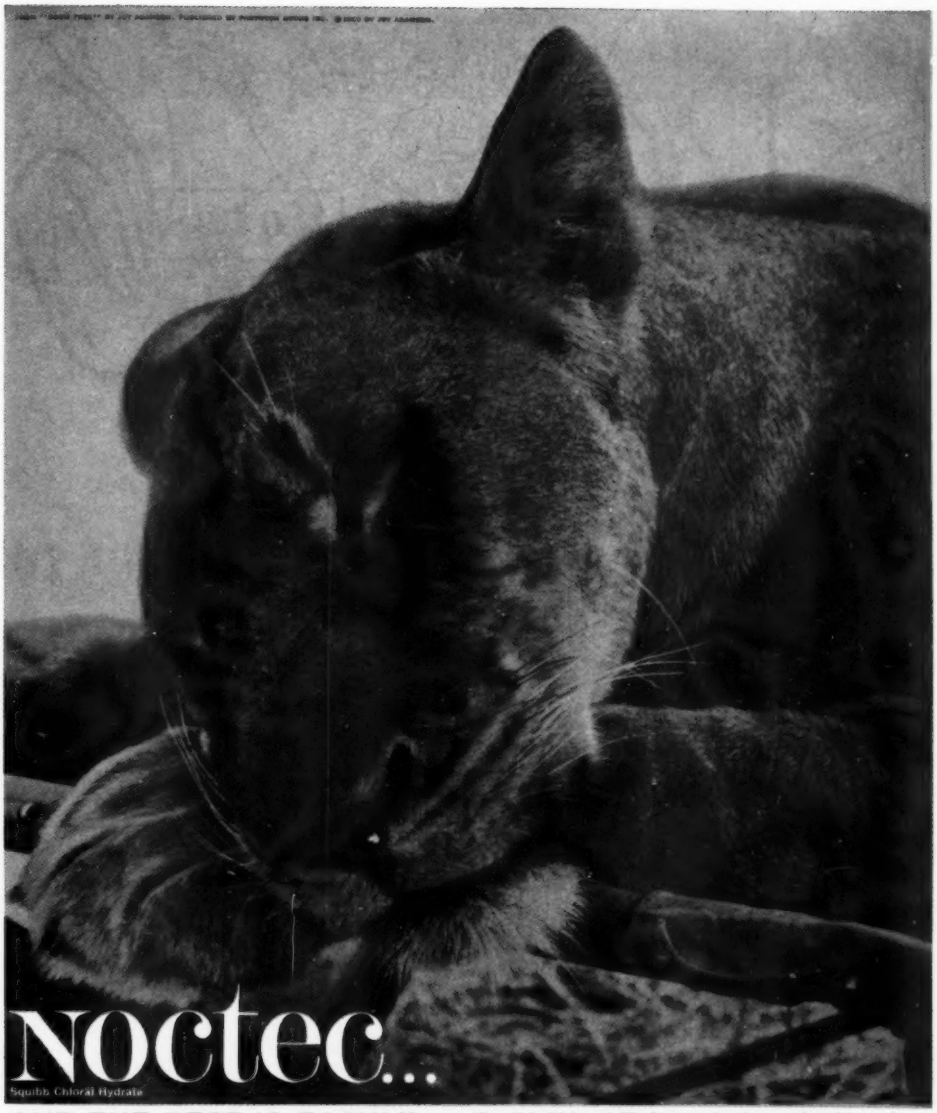
• HYPERINSULINISM

Q. A woman in her middle 30s has a mild case of hyperinsulinism which is proving difficult to control. She is 5 ft. 4 in. tall and weighs 180 lb. Her hunger is never appeased; she sleeps badly and is nervous. What treatment do you suggest?

M.D.—Ontario

A. Unappeased hunger in itself is not a characteristic symptom of hyperinsulinism, although it is frequently concomitant with anxiety or tension. Since the symptoms described generally are more consistent with an anxiety-tension state than with hyperinsulinism, the validity of the diagnosis should be tested. This requires (1) the demonstration of pathologically low levels of blood sugar associated with symptoms; (2) prompt and specific relief of both symptoms and low blood sugar values by the administration of glucose; and (3) induction of hypoglycemia under conditions of stress, such as prolonged fasting or exercise.

Genuine hypoglycemia ordinarily requires surgical exploration for the possibility of an insulinoma. However, if an anxiety state associated with excess appetite is diagnosed, psychotherapy and possibly treatment with one of the milder ataractic drugs would be indicated.



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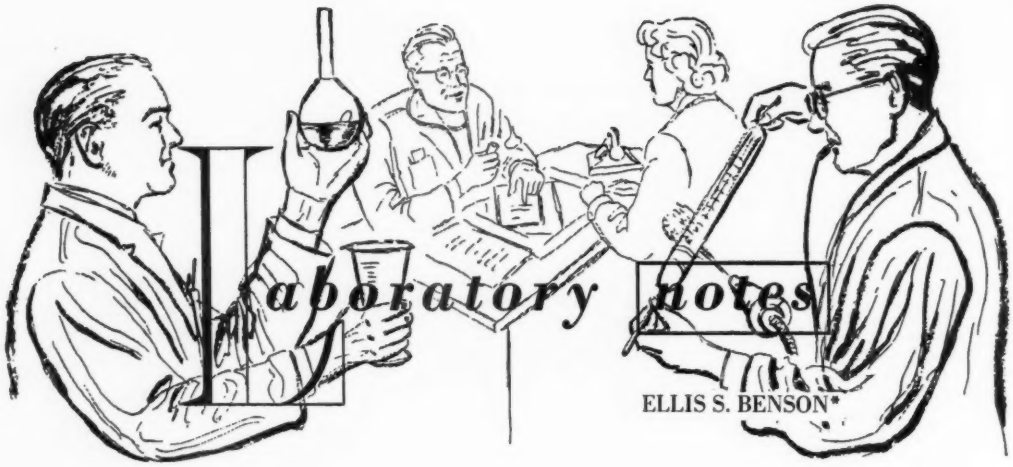

ELLIS S. BENSON*

Urine Amylase

LESLIE ZIEVE

University of Minnesota Medical School, Minneapolis

The evanescent nature of the elevation of serum amylase so characteristically related to acute pancreatitis places a definite limitation on our reliance on this test as a diagnostic tool. In this month's contribution, Dr. Zieve describes convincingly the advantages of the measurement of urine amylase in diagnosing acute pancreatitis.

Dr. Zieve is associate professor of medicine, University of Minnesota Medical School, and chief of the radioisotope service, Veterans Administration Hospital, Minneapolis.—Ellis S. Benson, M.D.

THE determination of serum amylase as a diagnostic test needs no advertisement. It has proved to be so invaluable in the diagnosis of acute pancreatitis that physicians have frequently forgotten that an elevated serum amylase may result from causes other than acute pancreatitis.[1,2] The most dramatic case in point is gangrene of the small bowel. Also, the serum amylase may fail to rise in the presence of pancreatitis, particularly the hemorrhagic variety. Elevated serum amylase is typically a reflection of regurgitation of pancreatic juice due to increased pancreatic ductal pressure; it is not a response to pancreatic necrosis per se, as is the case with certain other pancreatic enzymes such as desoxyribonuclease.[3] Pancreatic amylase also may be absorbed via the lymphatics from loculi (pseudocysts) or effusions (peritoneal or pleural) associated with episodes of pancreatitis.

LESLIE ZIEVE

Much of the amylase passing into the circulation is excreted by the kidney. Normally, the clearance of amylase is 2 ml. per minute.[4]

(Continued on page A-24)

*Director of Hospital Laboratories and Associate Professor of Clinical Medicine and Pathology, University of Minnesota Medical School, Minneapolis, Minnesota.

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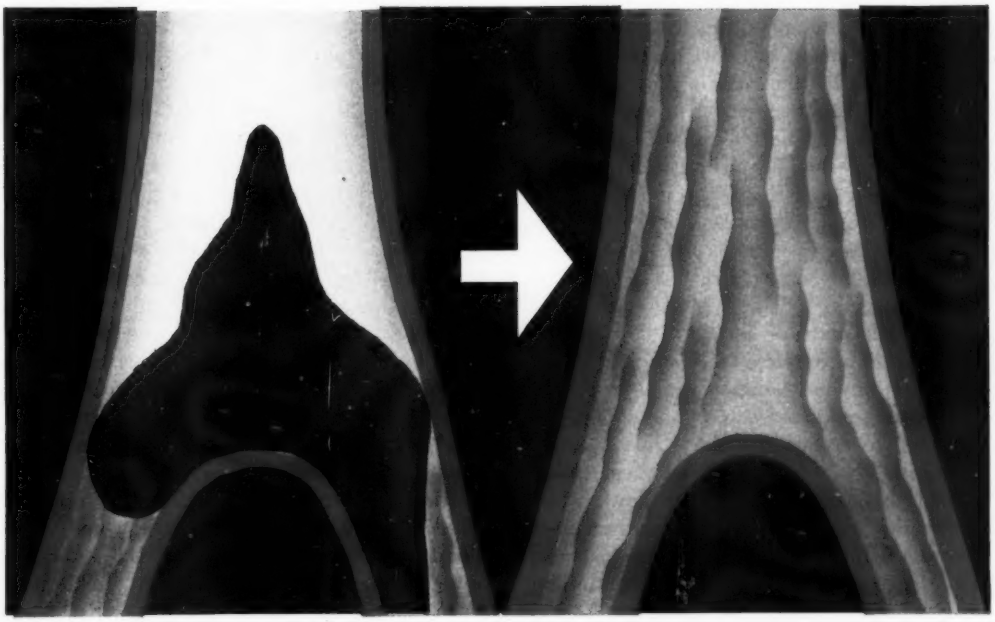

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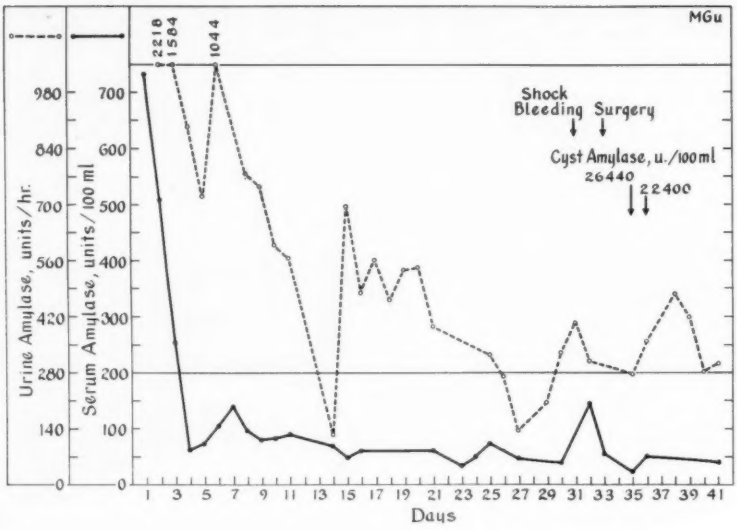

FIGURE 1. Serial changes in serum amylase concentration and urine amylase excretion rate in a patient with acute pancreatitis and pseudocyst formation.

It may be as much as 4 ml. per minute, or about 1/30 the normal glomerular filtration rate. In acute pancreatitis there is typically a threefold rise in the amylase clearance, which returns to normal in one to two weeks.[5] The mechanism of this increase in amylase clearance is unknown; however, we presume that it results from some effect of regurgitated pancreatic enzyme products on the kidney. Whatever its basis, there is a disproportionate increase in the urinary excretion of amylase during acute pancreatitis which is usually still evident when the serum concentration has returned to normal.[6,7] This is illustrated in figure 1, which portrays serial changes in the *concentration* of amylase in serum and in the *quantity* of amylase excreted in the urine in a patient with prolonged acute pancreatitis and pseudocyst formation. As is the rule in acute pancreatitis, the serum amylase concentration returned to normal within four days, while the quantity excreted in the urine remained elevated several weeks longer. In this instance, the presence of a pseudocyst as a continuing source of amylase accounted for the prolonged period in which the amylase excretion was abnormal.

Figure 2 illustrates four additional cases of acute pancreatitis in which there were an abnormality of urine amylase excretion in the presence of normal serum amylase concentration and a disproportionately greater abnormality of urinary excretion in the presence of abnormal serum levels. The typical lag between the return of serum concentration to normal and the return of urinary excretion rate to normal is illustrated in these patients.

Except when renal insufficiency with azotemia is present, in which case neither the serum amylase nor the urine amylase is valid as a rule, we have never observed an abnormal serum amylase level in the presence of normal amylase excretion. On the other hand, it is common to see an abnormal amylase excretion rate in the presence of a normal serum concentration. Generally, in an episode of acute pancreatitis, the urinary excretion of amylase is abnormal one to two weeks after the serum concentration has become normal.

The urine amylase excretion rate reflects sensitively the passage of amylase into the blood stream from sources of amylase storage or accumulation. An increase in circulating amylase which is insufficient to raise the plasma concentration beyond the normal range may be and usually is reflected in an abnormal excretion rate. We have noticed that

(Continued on page A-26)

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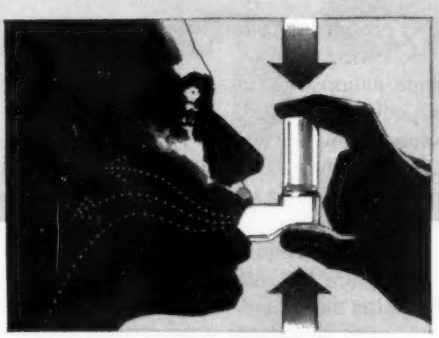

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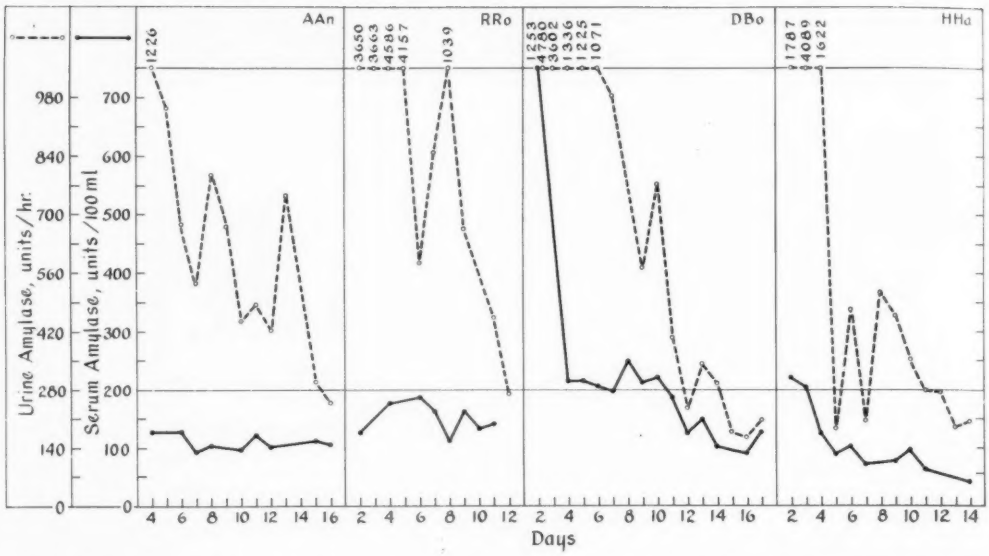

FIGURE 2. Serial changes in serum amylase concentration and urine amylase excretion rate in four patients with acute pancreatitis.

(Figures 1 and 2 are from Saxon and associates.[6])

changes in urinary excretion of amylase reflect sensitively the fluctuations in the clinical state of the patient with acute pancreatitis.

This great sensitivity of the urine amylase is particularly helpful in following the recovery of a patient with acute pancreatitis in whom the clinical and nonspecific laboratory findings become normal before the pancreatitis has subsided completely. However, this sensitivity also presents problems of interpretation in the fresh case in which there is, at most, mild elevation of amylase excretion. Values up to 1000 units per hour are the rule in patients with acute cholecystitis and cholelithiasis and in some patients with recurrent vomiting. Whether or not a mild pancreatitis is present in such cases, as in many cases of penetrating peptic ulcer in which there are such slight elevations, is uncertain. The patients with unequivocal clinical pictures of acute pancreatitis associated with the usual rise in serum amylase concentration almost invariably have urinary excretion rates of over 1000 units per hour, and these rates may run over 10,000 units per hour. Those non-pancreatic diseases in which an elevation of serum amylase is misleading also will show misleading rises in urine amylase, except in the presence of renal insufficiency.

If the determination of urine amylase has some useful advantages over that of serum amylase, why is it not used more extensively? This, I believe, stems from the fact that confusion in the earlier writings on urine amylase has left its imprint. A distinction often has not been made between urinary *concentration* of amylase, which varies with urine volume and is an erratic measure, and urinary excretion rate, which is the sensitive reflector of amylase released into the circulation. It has been claimed that urinary excretion simply parallels the serum level. This parallelism is generally true; however, the urinary excretion curve of abnormality is shifted to the right by a week or two, providing evidence of abnormality when the serum curve has already become normal. Technically, a little more care is needed in measuring amylase in urine, because the great fluctuations in urine concen-

(Continued on page A-28)

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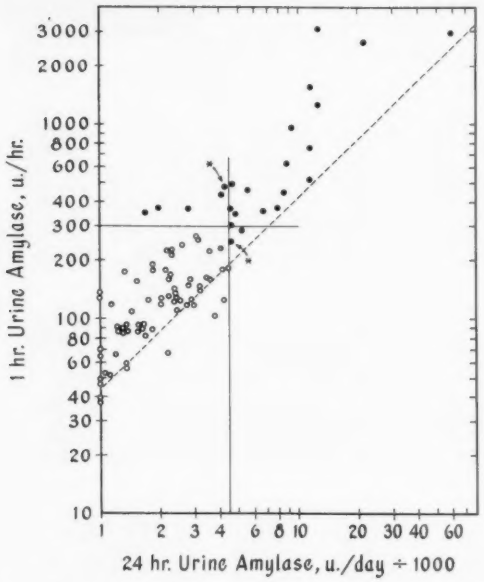

FIGURE 3. Correlation between one hour and 24 hour amylase excretion rates. Open circles represent normal persons; closed circles represent patients with mild acute pancreatitis. Horizontal and vertical lines indicate limits of normal for one hour and 24 hour urine amylase excretion, respectively.

The broken line indicates values that would be obtained if the excretion rate observed in one hour samples were maintained for the entire 24 hour period. This line was constructed by taking arbitrary values of the ordinate and multiplying each by 24 to obtain a corresponding value of the abscissa. Asterisks indicate two values obtained on the same patient on two consecutive days.

All one hour urine specimens were collected in the morning in the normal subjects and at various times during the day in the patients with pancreatitis.

tration, compared with serum, require the selection of an appropriate dilution of urine for purposes of the analysis. Also, it is less trouble for the nurse or physician to obtain a blood specimen than to ensure an accurate urine collection.

Some[7] have thought it necessary to require a prolonged period of urine collection (up to 24 hours) in order to obtain a valid measure of the rate of amylase excretion. Such long periods of urine collection are undesirable when one is urgently seeking a diagnosis. They are also unnecessary, since a single hour's excretion rate, assuming adequate urine flow, gives essentially the same information as a 24 hour collection, as shown in figure 3. If anything, the short period of urine collection is better, since errors of collection are less likely. The three cases in figure 3, falling well within the normal range for 24 hour urine collections while being abnormal on the one hour analysis, are probably instances of incomplete 24 hour collections. The fact that the broken line in figure 3 falls below most of the points indicates that the nighttime amylase excretion is less than that in the daytime, so the net excretion rate over 24 hours is less than the usual one hour excretion rate observed during the day. As a matter of practice, we have found it convenient to collect urine over a two hour period after forcing fluids briefly, in order to minimize errors of urine collection.

In summary, measurement of the urine amylase excretion rate is a useful and simple procedure that yields valuable information when determination of the serum amylase concentration does not. It is a sensitive reflector of the clinical and even subclinical state of the patient with acute pancreatitis, and slight elevations, although indicative of an abnormality, must not be overinterpreted. Those nonpancreatic diseases giving rise to an abnormal serum amylase concentration also will yield an abnormal urinary excretion rate, except in the presence of renal insufficiency.

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What's happening in Medicine ?

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

SURVIVAL IN BREAST CANCER

Sectional meeting, American College of Surgeons:

- Favorable response to treatment of breast cancer is sufficiently frequent to warrant an all-out effort. A 30 year study of all cases of breast cancer at the University of Pennsylvania Hospital showed an absolute five year survival rate of 36 per cent. For the 229 patients treated in the last 10 years, the five year cure rate was 41 per cent. Patients free of cancer for 23, 22 and 19 years also have been found.—Drs. Charles K. Zug, III and Charles H. Cretzmeyer, Jr., University of Pennsylvania School of Medicine, Philadelphia.
- Morbidity from diverticulitis will remain high unless surgical intervention is used more often in cases without complications of obstruction, perforation or fistula. If the indications for surgery were broadened, only primary resection would be required. Surgery is indicated for patients with a history of two or more attacks of diverticulitis, for those who have recovered from an acute attack but have a palpable mass in the lower left quadrant, and for those with a significant narrowing of the sigmoid colon after symptoms have subsided. —Dr. B. P. Colcock, Lahey Clinic, Boston.
- Erythrocytes have shown an in vitro recovery rate of 77 per cent after three years of storage following quick-freeze. The cells were first mixed with lactose and glucose. Freezing was carried out at minus 70° C. for 15 to 30 seconds.—Dr. Max M. Strumia, Bryn Mawr Hospital, Bryn Mawr, Pa.

MEDICAL ETHICS TEST URGED

Congress on Medical Education and Licensure:

- Knowledge of medical ethics and of the medical practice act of the state should be required as part of the licensure examination. Present control of discipline by both state boards and local medical societies is inadequate. Nearly one-half of the medical schools surveyed give no lectures on medical ethics and discipline.—Dr. Harold E. Jervey, president, Federation of State Medical Boards of the United States.
- A nationwide survey showed that a majority of house physicians in the United States desire more teaching in relation to service time. About one-fourth of the house officers in 164 hospitals surveyed said they should be learning more. In closely affiliated hospitals, the chiefs of the services were the physicians most admired by the house officers. As one moves to the hospitals with less-close affiliations, the influence of the chiefs declines and is replaced by that of the attending physicians.—Dr. Patricia Kendall, Bureau of Applied Social Research, Columbia University, New York.

Hypothermia-Hyperthermia for Cancer

Society of University Surgeons:

• Combining hypothermia with hyperthermia has permitted use of alkylating dosages three to four times larger than safe dosages administered systemically in abdominal perfusion for cancer. The hyperthermia heats the extracorporeal blood to 41° C. before perfusion through the isolated abdominal area, while the general body temperature is reduced to 31° C. The alkylating agent is introduced at five minute intervals into the inflow catheter of the perfusion unit. This procedure produced profound relief of pain in a majority of 25 advanced cases. No evidence was seen of electrolytic disturbance or damage to the function of the gastrointestinal tract, kidneys or liver.—Dr. William W. Shingleton, Duke University School of Medicine, Durham.

• Circulating pancreatic antibodies to human pancreatic homogenate were found in the diluted serums of 15 of 16 patients with acute or chronic pancreatitis. It is interesting to postulate that in the acute phase of the disease the patient disseminates particles of tissue antigen which in turn stimulate the body's immune mechanism to produce antibodies.—Dr. Eric W. Fonkalsrud, University of California School of Medicine, Berkeley-San Francisco.

• There appears to be a short, definite period when antibiotics are effective in treating dermal or incisional lesions in animals. It begins when bacteria gain access, and lasts only about three hours. Maximal susceptibility to antibiotic action is found when the drug is in the tissue before the bacteria arrive.—Dr. John F. Burke, Massachusetts General Hospital, Boston.

Psychiatry by Nonpsychiatrists

Clinical Conference, Chicago Medical Society:

• There is no reason why many young physicians should not be interested in participating in some variety of psychiatric practice, whether or not they plan to achieve complete specialization in the field. Ignoring this potential reservoir of psychiatric man power is foolish and wasteful.—Dr. C. H. Hardin Branch, University of Utah College of Medicine, Salt Lake City.

Asepsis in Chemotherapy

Seminar, American Cancer Society, Inc.:

• A sterile hospital environment has been established for patients from whom bone marrow has been temporarily removed during chemotherapy. Blood pressure, pulse, temperature, respiration and electrocardiographic data are recorded by remote technics. The patient eats food, smokes cigarettes, and reads newspapers that have been sterilized.—Dr. David M. Hume, Medical College of Virginia, Richmond.

• Prophylaxis with thio-TEPA following surgery has reduced the recurrences of breast cancer by one-half in the first 26 months of a cooperative study of 718 women in 23 hospitals.—Dr. George A. Moore, Roswell Park Memorial Institute, Buffalo.

• Leukemic cells from the bone marrow of a two year old boy were found to contain 97 chromosomes. Cells in the child's other tissues carried the normal complement of 46 chromosomes.—Dr. Avery A. Sandberg, Roswell Park Memorial Institute, Buffalo.

• Breakdown products of DNA (desoxyribose nucleic acid) can be mixed with a supplement to delay the onset of tumors in the cancer-prone C3H strain of mice. The name DD has been given to the substance, but its nature is unknown. Addition of DD provokes antibody formation.—Dr. Werner Braun, Rutgers University, New Brunswick, N. J.

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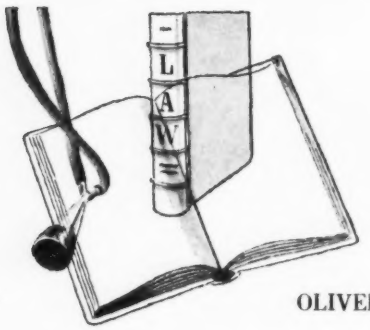


Forensic Medicine

OLIVER C. SCHROEDER, JR.*

The Medicolegal Forum: Traumatic Neurosis

Editorial Comment

Lawyers are concerned with resolving personal injury cases. One method is by settlement negotiations. An overwhelming number of these cases (95 per cent or more) are settled. The technics of the settlement process are displayed in this forum. The medical issues are crucial, but other facts and opinions also shape the settlement discussion. Medical practitioners should know how the medical materials are used in settlement and what other materials influence the process. Lawyers, too, have great interest in the technics of other legal counsel in this area.

The following dialogue brings these matters into focus. It is a capsule review of an actual demonstration presented at an institute of the Law-Medicine Center in Cleveland. Two able trial counsel of the Cincinnati bar were the participants: Walter C. Beall (identified as "P"), representing the injured plaintiff, and Ambrose H. Lindhorst (identified as "D"), representing the defendant bus company.

MRS. X is a 52 year old woman who, prior to an accident, had been in good health. She had had no previous hospitalization other than for childbirth. She had had no disabilities, and had been exceedingly active. While she was sitting in her car, a bus struck the back of it. According to her complaints, she rapidly degenerated from being very healthy to being almost unbelievably sick. Mrs. X showed no symptoms of a slipped disk; a myelogram revealed negative findings, and there was no indication of a fracture.

Two medicolegal issues arise in this case: (1) Is there some pathologic disorder that produces pain, the extent of which is not clear but which, in any event, is not of any great degree? (2) Is there traumatic neurosis?

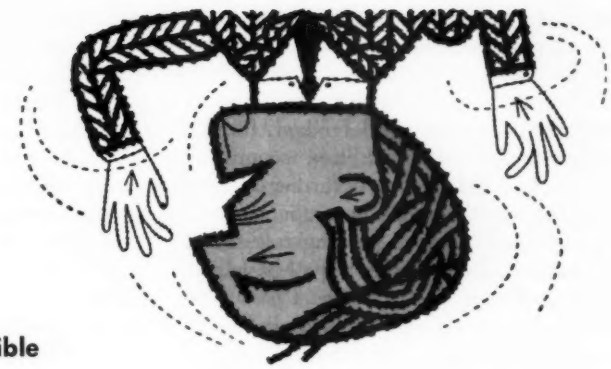
Discussion Between Counsel

D: I would assume that in coming to my office this afternoon you have concluded that this case is one of liability. Now, I'd merely like to suggest to you that nothing is further from the truth.

P: But the fact remains that this car stopped behind another car. Both drivers said that there was a red light. Now, I know from the deposition that the bus driver said that the light was green. Everybody else on all these streets was stopped or was moving crosswise. So, I suppose everyone was in error but him. I don't think your no-liability idea means a

(Continued on page A-50)

*Director, Law-Medicine Center, and Professor of Law, Western Reserve University, Cleveland, Ohio.



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whole lot as to my woman client, who was merely a passenger.

D: The driver of the car that stopped suddenly in front of your client's auto certainly should have been a named defendant. I'd like to suggest further that in addition to omitting one of the two defendants, a further fact on the liability is that while no imputation of negligence from driver to passenger arises, it does remain that the operator of this vehicle in which your lady was riding as a passenger was her husband. He did not signal; he did stop suddenly. If that is true, legally, we may not recognize the fact but, practically, in the courtroom, we know that juries impute to wives their husbands' negligence.

P: Well, before you go any further on imputation, if we're going to discuss settlement, I want to dispose not only her case but also his. That involves roughly $3500 in special damages. We'll talk about the husband, too, because, as far as I'm concerned, even if you dream up something, my man stopped behind another car, and he had plenty of time to stop. There's no argument that the two cars were stopped when your bus hit us. You ran about 10,000 lb. of bus at about 20 miles an hour right up the back end of our car.

D: I don't want to impugn your attitude toward this case but, in addition to very limited liability, it seems to me that you really don't have any injury. What you've got here is a freak female; or, perhaps it might be said that she bruised her knee slightly. I don't think we need debate the subject that she actually had 23 different doctors. Now, either she's a freak or there is something else wrong with her.

P: The significant feature, as far as I personally am concerned, is that the first specialist she was sent to was a client of yours. He is a very fine orthopedist whom you personally represent. He treated her for four months. If she wasn't really injured, your good client has made a lot of money off my good client.

D: I don't want to be held responsible for all of the complaints that you might have against the world of orthopedic surgeons. Just because I represent this one is no reason for him to make a correct or an incorrect diagnosis in this case. As a matter of fact, you read his report. The first orthopedist she visited wrote to the attending physician, and he said, "My goodness, if we tell this lady that she isn't hurt, we're going to cause her more harm than good, so I suggest that we give her some therapy. We don't know exactly what's wrong. We know that she has a degenerative hip condition."

P: Does all this go along with the fact that at the end of the four months he said to her, "Lady, if you don't get well, I'm going to operate on you"?

D: Well, of course, that goes along with the doctrine that he didn't know just what was wrong.

P: But he was going to operate on her if she'd stand still for it.

D: There was no conclusion drawn here that surgery would take place. Incidentally, before we get into a lot of hash about what I think of your lady, what kind of money have you got in mind?

P: Well, it isn't so much a question of what I have in mind as it is a question of what my client will agree to.

D: Well now, just a minute! Are you going to evaluate this case? Or are you going to be like a lot of lawyers who are led around by the nose?

P: Really, both of us are going to be led around by the nose. Neither one of us is going to settle this without our clients' approval. There's no point in kidding ourselves.

D: Now, just a minute. I make recommendations to my bus company. I expect when they hire me that they'll follow my recommendations. If you're going to let this freak female put a monetary value on this case, we can't settle it.

P: You and I both know that this case has been going on for seven or eight years, and she's stuck at $25,000. I myself would be willing to take the recommendation of an offer from you of $17,500—with my blessings.

D: Really, this case has a value of from somewhere around $1500 to perhaps $2500. Conceivably, I'd be willing to go to that extent. I know that what you have here is a lady 52 years of age with a myriad of com-

(Continued on page A-53)

plaints. Now you scheduled these depositions from Dr. B., who I think is probably one of the outstanding neuropsychiatrists in the United States, and I mean that sincerely.

I want you to turn to Dr. B.'s deposition. What you have here is a menopausal female. She thinks she's losing the love of her husband. She can't make the country club crowd, and she is using our little bus company here to try to get well.

I asked, "Did Mrs. X tell you that she had entered into the period of menopause prior to this accident?"

Dr. B. answered, "Yes."

"In your judgment, she was at some point in the menopausal area?"

"Yes, she was fairly well along."

"Isn't it a fact, Doctor, that hysteria, in any one of its many different forms that you might describe as such, sometimes accompanies menopause?"

"That is correct."

"And isn't it true, Doctor, that hysteria as you found it in this woman can come from any one of a number of causes—I mean, other than trauma?"

"Yes."

P: You took advantage of a doctor who did not know the case. But the fact remains that this doctor testified specifically that in view of the fact that this woman had no prior physical ailments, in view of the fact that there was no prior trauma, and in view of the fact that we had a single event of trauma he could say in his own good conscience that hysteria is the result of the automobile accident and not of something else.

D: I know more about your client than she knows about herself. Let me suggest first that among other things she is now 52 years old. Her social friends for the past eight or 10 years have financially gone beyond her. All her former friends and friends of the family are now members of the W. H. Country Club. She and her husband haven't been able to make the ripple financially. That has caused a depressive thing which I consider to be one of the present elements of her hysteria.

Secondly, I think she now feels that she is losing the love of her husband. I think she's looking for an excuse. I think long before this accident she was a morally weak woman. I don't think she could face up to the frank reality of life. I don't think that all of this hysteria should now be charged to one traumatic event when we have a female, morally weak, socially insecure.

Dr. B. will prove these points in his deposition. I asked him, "In other words, if a person desired a sympathetic reaction from the people around her because of an unhappy home life or some difficult situation encountered in ordinary everyday living, the situation could develop from that sort of circumstance, could it not?"

"Yes, if it were done unconsciously. If it were done consciously, it would be malingering, which would be a volitional assumption."

"In other words, Doctor, the true difference between hysteria and malingering is that the hysteriac is fooling himself and the malingerer attempts to fool others."

"That is correct."

"In some instances, Doctor, is it not true that there is a combination of hysteria and malingering?"

"Very often."

"Doctor, would you describe such a person as being morally dishonest?"

"I don't believe I could make a moral judgment on that."

"If a person attempted to fool others by malingering in order to recover money in excess of what was warranted under a given situation, it would be morally dishonest, would it not?"

"According to my moral system, it would be, yes."

"Doctor, is it a fact that compensation or 'greenback neurosis,' as it is sometimes referred to, is sometimes partially hysteria?"

"Yes, sir."

P: But you didn't go far enough. You also asked, "And do we understand that the definition of compensation neurosis is an inordinate desire for money?"

And the doctor said, "No, sir, I regard it in terms of how the patient might feel about it. The sum might seem inordinate to one and

(Continued on page A-54)

yet seem niggardly to the patient. But I don't believe I can agree that it was an inordinate desire for compensation."

What you breezed over so casually, though, is the fact that every time you asked one of these nice theoretical questions the doctor indicated that this woman was acting unconsciously as the result of a traumatic neurosis.

You left out your last question: "Certainly you would describe the actions of Mrs. X as being unconscious, would you not—or done unconsciously?"

The doctor answered, "I was of that opinion. I did not believe that she was volitionally behaving in this fashion."

D: As a matter of fact, she could have gotten this hysteric condition from going to 23 different doctors.

P: She went to 23 doctors because she became hysteric.

D: Dr. B. admitted that a physician himself could cause hysteria in a patient. He said that it is sometimes not uncommon for a physician either to exaggerate or to extend his diagnosis out of proportion to what it should be. So I suggest that since she went to 23 different doctors and since her own deposition indicates that she was critical of at least half of them and suggested that at least half didn't know what they were doing perhaps this hysteria came from the very doctors who were treating it.

She never told you about what happened to her in 1944, did she? She hurt her back in 1944. She never told Dr. B. anything about it. I doubt that she's ever told you about it.

P: Well, it's utterly insignificant; it makes no difference.

D: Did you ever check into her family background? She had a sister who died at age 40 and who had epileptic seizures throughout her life. She had another sister who had hypertension. Her mother also had hypertension and died from heart disease.

P: Now, do I get this right? Do you think that you shouldn't pay her because her husband is not making enough money and her mother died of a heart attack at age 74?

D: No, I don't say that I shouldn't pay her for those reasons alone. I want to suggest that when you have a condition of traumatic neurosis (your own doctors say that the plaintiff is a hysteriac) I consider the family background of the utmost importance. And when I see this family background, I see a woman who has the same characteristics as two of her sisters and her mother. I find that grossly significant because you are trying to take all of this symptomatology and charge it to my bus company.

P: After considering a bus company with all kinds of money and your complaint that her mother was sick at the age of 74, I don't think the jury will believe your sad story.

Let us look at Dr. J.'s deposition. He was asked, "Did you find any causal connection between the degenerative disk disease in the lumbosacral area and the accident in which Mrs. X was involved on September 6, 1952?" He replied, "I believe that the degenerative disk disease was either aggravated or initiated by the accident."

Dr. J. was then asked what examination was made. He said that it was what would be termed a general medical examination, which means a medical study of all organ systems of the body.

"What were the findings?"

"A diagnosis was made of essential hypertension, posttraumatic depression and anxiety psychoneurosis."

Finally, he was asked his opinion about all this. He replied, "My diagnosis was reactive depression. A reactive depression means a mental depression which occurs in relation to or in response to some significant life event. Utilizing the history that she gave, I made the assumption that her unquestionable depression was in reaction to the accident."

The doctors at M. Clinic said that (1) she did suffer physical damage; (2) this brought on a traumatic neurosis, and (3) the traumatic neurosis was the result of the accident.

In the event of trial, we would be able to establish very clearly through a series of people who knew her very well that she was exceedingly active in the Y.M.C.A. She participated in bazaars; she set things up and she did all kinds of work. She was very active in

(Continued on page A-56)

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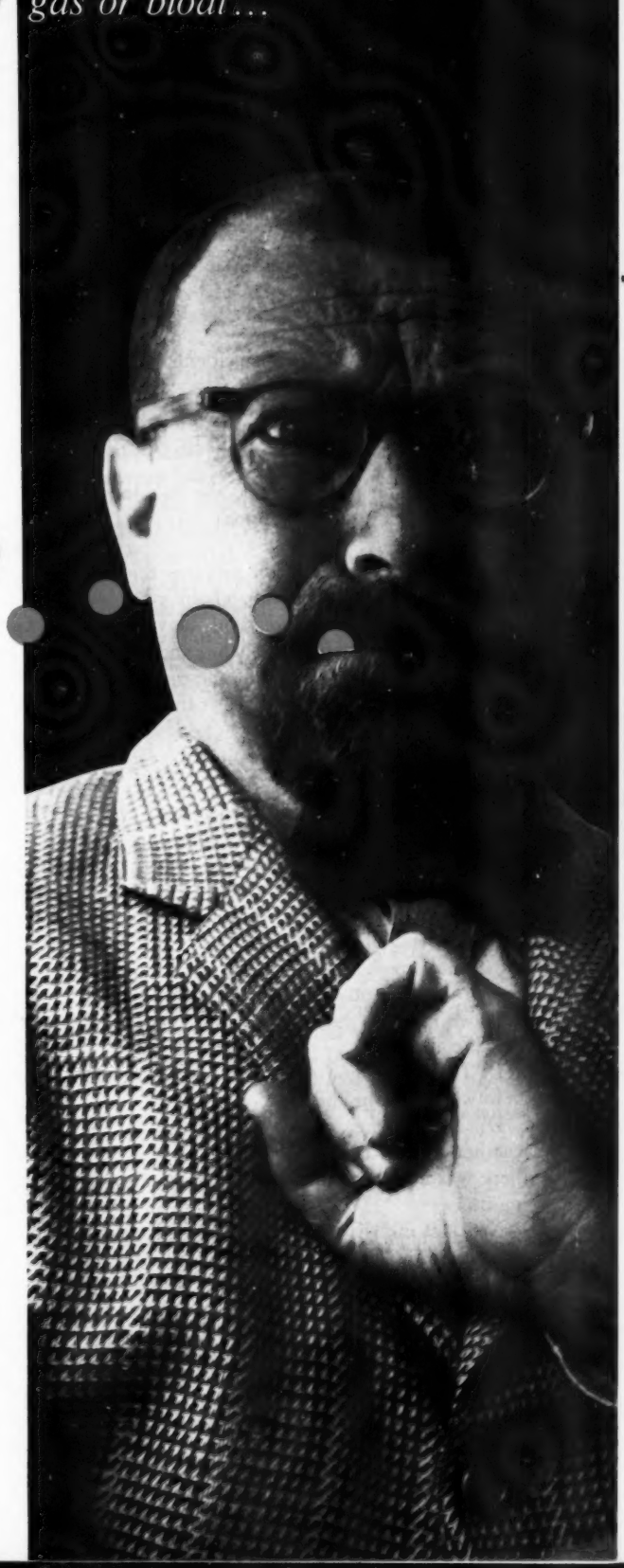

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"Use of Silicone in the Treatment of Intestinal Gas and Bloating," J.A.M.A., 174:2052, (Dec. 17) 1960.

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her church. She had all kinds of obligations. She led a very active life. She had all kinds of people coming to visit her, and she went out and played bridge. She walked all the way to the grocery store and back, carrying her packages. It was 2 miles to the grocery store.

D: What about her yard work?

P: Yard work and all; she did everything around the house.

D: Before the accident?

P: Absolutely.

D: What about after the accident?

P: After the accident, not only was she unable to do yard work or housework, but she wasn't able to drive. She had to be helped up and down a flight of steps.

D: But, after the accident, she couldn't do any yard work either, I suppose.

P: Absolutely.

D: I've got some motion pictures that will give you a little information about your own client. One picture shows your lady cutting her front lawn. She has slacks on, and she certainly hasn't lost any weight. The only reason that we didn't get more movies is that the dog is smarter than the plaintiff. The dog found one of the young men from my office before she did.

Incidentally, another picture shows that she not only cuts the lawn but also cleans the mower. I want to compliment her. That's more than I do myself. But it shows that she has the capacity not only to push the mower but also to stoop over. She's bending down and kneeling on one knee. Another picture was taken to show that she cuts not only the level part of the lawn but also the embankment. That poor, sick female!

P: I presume you took an accurate record as to what day she did this?

D: Date, time, hour; we also have the weather reports from the weather bureau, and there was a witness to the photographer's taking it.

Now, let me read the last paragraph of the deposition of Dr. W., who examined Mrs. X for us. "There is no doubt in my mind that the sacroiliac injury that the patient admits receiving in 1944 was actually an injury to the fifth lumbar intervertebral disk. In addition, I believe that the injury which this patient received in September of 1952 should be considered as only an aggravation of a condition that existed at the lumbar level. If this patient's demands appear to you to be excessive and unreasonable, then I believe the final settlement should be referred to court action."

P: Dr. W. found that this woman had spasms of the muscles in her back. Do you imagine she faked that?

D: No, I recognize that muscle spasm is an objective symptom, but I further believe that the muscle spasm has been in her back for a period of years. I think that it predates the accident.

P: Now, a period of seven or eight years is a long time for someone to go through this pain and suffering. You can ridicule the number of doctors that she went to, but the most significant feature is that she finally went to Dr. K., who is also an orthopedist. He was the first to determine the cause of the trouble. As she said, the others apparently didn't know what they were doing.

D: What was his number on the medical hit parade? Was he number 22 or number 23?

P: I would imagine he was pretty close to your number 23. But the fact remains that he finally made a diagnosis of the degenerative arthritis from the cervical spine into the lumbosacral spine. The injury was superimposed on this. She had this arthritis before, and there was then an injury. Dr. K. treated it. The x-rays that he obtained show that the section involved is from the pelvis up roughly into the low end of the thoracic spine. While it may not be entirely clear, there is a very marked scoliosis. Not only Dr. K. but also the original orthopedist whom you claim as a client and the one whom you claim as a retained doctor found the muscle spasm. The x-ray confirms that the muscle spasm pulls the spine out of line. Now this spasm is due to just one thing—pain. There's the only thing I want to talk about—not what you conceive to be the source of it, but what has, in fact, happened. This woman was healthy. She had an accident. The only question is whether or not she has pain as a result of the accident. Does she have any

(Continued on page A-59)

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discomfort? The x-ray shows clearly that she has the spasm that arises from the pain. It is bad enough to pull the vertebrae out of line. Secondly, the smaller x-ray shows the cervical spine along all the vertebrae with arthritis. This precludes the possibility that she is faking pain.

D: Are you suggesting that the arthritic condition was caused by this accident?

P: No, solely that it was aggravated.

D: Are you going to try this on a typical sequence approach of before and after?

P: To the nth degree. We happen to have these four magnificent witnesses who will come in and testify that prior to this accident she was very healthy. After this accident she was in a great deal of pain and couldn't do all kinds of things; in fact, there was very little that she could do. Maybe you could laugh that off, but one of the witnesses happens to be a schoolteacher, and, while my experience is very brief compared with yours, juries believe schoolteachers. We have a most magnificent coincidence; the county health commissioner is also one of these witnesses. He will come in. Everybody knows him from reading his articles in the paper for years. He's going to tell what a healthy, happy, pleasant woman she was before, and how after the bus hit her she suddenly became a semi-invalid. She wasn't in pain before; she was healthy before. She had this accident. There is no dispute among the doctors that it aggravated a pre-existing condition. There is no dispute that she has a traumatic neurosis now.

D: Well now, are you telling me that you've given me your rock-bottom figure? I'll tell you what my opinion of this case is. I think it has a value not in excess of from $5000 to $6500. I recognize that the out-of-pocket expenses are $3500. What is your bottom dollar?

P: $12,500.

Verdict

No settlement was effected. This case went to trial. The jury was out about four hours; the verdict was $10,000. A motion for a new trial was filed, but the court ordered a reduction in the verdict to $8000, which the plaintiff accepted.

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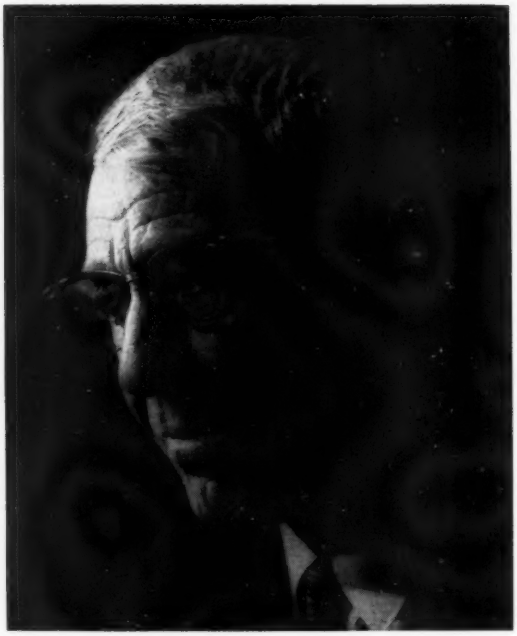

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DOSAGE: Adults and children over 12, one or two capsules. Children, age 6 to 12, one capsule. Administered at bedtime for 2 or 3 days or until bowel movements are normal. Supplied in bottles of 30 and 100 soft gelatin capsules.

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Radiology FOR PRACTICING PHYSICIANS

Aspiration and Inhalation Pneumonias

PAUL C. HODGES*

SILICOSIS and beryllium disease, which I discussed in this column in September and October, respectively, are, of course, inhalation pneumonias. This month's discussion will be concerned with the pneumonias that follow the aspiration and inhalation of certain substances other than particles of silica or beryllium. In some of these, the symptoms are as severe as the x-ray findings indicate; however, in others, with equally alarming x-ray findings, the symptoms are so mild as to belie a diagnosis of "pneumonia" and suggest to the timid examiner the supposedly less definitive term "pneumonitis." Only those who read little and write less harbor the misconception that it is pedantic to be concerned with terminology. The literate know that only with meticulous regard for the meaning of words are human beings able to communicate effectively with one another and that communication is particularly difficult in medicine. Familiarity with dictionaries is important, of course, but even the largest and best of these have their limitations, and desk-sized medical dictionaries obviously cannot devote much space to the listing of semantic nuances.

Literally, "pneumonia" means "pneumonitis" and "pneumonitis" means "pneumonia," but unfortunately to some physicians the former term connotes the full-blown clinical entity of lobar pneumonia or bronchopneumonia, the latter a clinically less important type of inflammatory lung disease. It frequently happens that a lesion seen in chest x-ray films and interpreted as "pneumonia" eventually proves to be quite noninflammatory, but it is a breach of intellectual integrity to contend that the substitution of "pneumonitis" for "pneumonia" would have avoided or at least lessened the degree of error. In my opinion, physicians would do well to drop "pneumonitis" entirely and recognize that the "pneumonias" exhibit wide variation in etiology, anatomic distribution, degree of severity, and prognosis.

Aspiration Pneumonia

If the aspiration of liquids, including semiliquid food and vomitus, invariably provoked bronchopneumonia, the disease would be extremely common and few of us would have escaped it. Probably no child fails to aspirate

*Emeritus Professor and Chairman, Department of Radiology, University of Chicago, Chicago, Illinois.

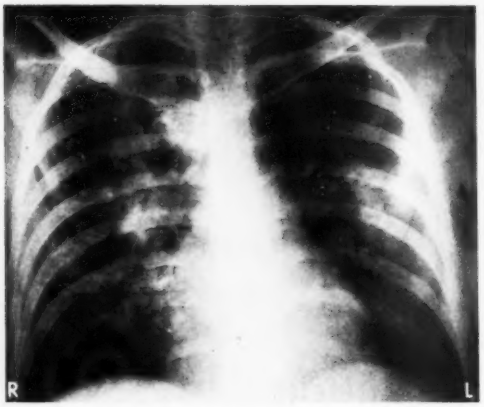

FIGURE 1. Bronchopneumonia caused by aspirated vomitus.

FIGURE 2. Fatal cod-liver oil pneumonia.

small amounts of milk during nursing or vomitus during the vomiting which accompanies so many of the acute diseases of infancy and childhood, and patients being examined in an attempt to determine the cause of dysphagia commonly aspirate some of the barium suspension they are attempting to drink. However, it is rare indeed that such accidents are followed by pneumonia.

Work on experimental pneumonia has shown why aspiration pneumonia does not develop more frequently. It does not suffice to soil an animal's lung with infectious material; one must provide some sort of plug to hold it in place for a considerable period. When aspirated material is not locally irritating, not particularly tenacious, and not present in overwhelming amounts, particularly when the subject is conscious and able to stand and to cough, powerful physiologic protective processes assure clearing of the field promptly enough to avoid serious consequences. It is the infant or the unconscious or otherwise incapacitated adult who is in danger of aspirating and retaining enough vomitus and driving it deeply enough into the bronchial system to produce pneumonia. Figure 1 illustrates this condition in a 23 year old woman who aspirated vomitus during delivery. The lesions are bilateral, and their distribution is not unlike that seen in nu-

EXPLANATORY NOTE

The two sides of an x-ray film are physically identical, but it is conducive to orderly thinking to adhere to convention in putting films on a view box or reproducing them in publications. If one stereoscopes (failure to do so imposes a serious handicap particularly in examination of the chest), he has no choice, and must employ the convention of looking at them "as the x-ray tube saw them." In the case of the usual chest film made with the patient facing the film, this means that the right side of the chest will lie at the observer's right hand and since approximately half of all the films made in our laboratory are stereoscopic, we tend to view all films by that convention. A convention of some sort is desirable because of the subtle though sometimes highly significant differences in appearance, depending on whether the patient was rayed face to film or back to film. Clinicians, in particular, tend to look at all chest x-ray films as though they were looking at the patient's chest forgetting that they also look, listen and percuss his back, and that the findings are different in the two positions.

In the five x-ray films reproduced here, figures 1 and 2 are shown with the right side of the chest at the reader's left hand, because for special reasons these two patients were rayed back to film. Figures 3, 4 and 5 are shown with the right side of the chest at the reader's right hand because those patients were examined in the more conventional face-to-film position.

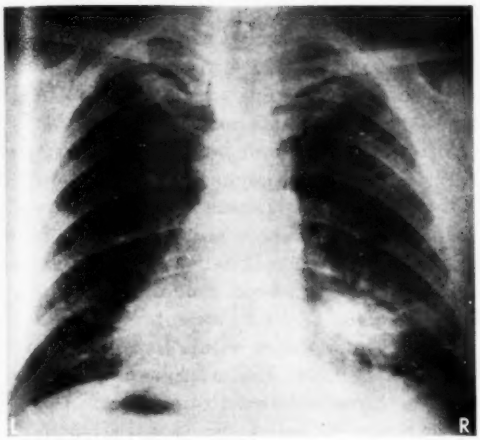

FIGURE 3. Mineral oil pneumonia, which was mistaken for pulmonary neoplasm.

merous other diseases. In such a case, it is the history, symptoms and physical findings that really make the diagnosis, but the x-ray examination is essential for determining extent and distribution. As in all acute pneumonias, x-ray findings do not appear until some hours after the symptoms occur, and they may persist some days after recovery is well advanced.

Cod-liver Oil Pneumonia

The lipid pneumonias vary greatly in severity, depending on the nature of the aspirated oil.[1] Cod-liver oil is a particularly noxious agent. Figure 2 shows atelectasis of the upper lobe of the right lung of a five month old boy who had paroxysms of coughing after aspirating part of the dose of cod-liver oil that was being administered to him. Fever developed, and the child died 12 days later. Lipid pneumonia and a lung abscess were found at autopsy.

Even those inorganic oils which are practically nonirritating to lung tissue are able to produce pneumonia by gradual accumulation and foreign-body reaction, but some organic oils, and particularly cod-liver oil, also produce severe local irritation. Many inorganic oils also are toxic to tissue, and fatal pneumonia in infants who have aspirated kerosene remains all too common in spite of reiterated warnings of the danger of leaving the material where children can get at it.

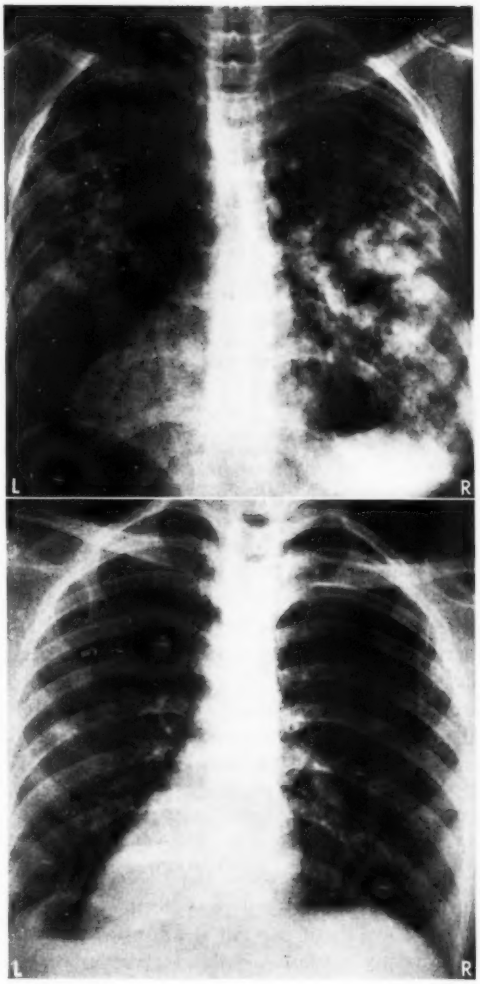

FIGURE 4. *Top.* Acute chemical pneumonia caused by inhalation of a spray for Christmas trees.

Bottom. X-ray made five days later showing complete recovery.

Mineral Oil Pneumonia

Liquid petrolatum and similar lightweight mineral oils, refined to the point where they are tasteless, are so bland in regard to their effect on bronchial mucosa that when aspirated in moderate amounts they do not evoke the

FIGURE 5. Lesions caused by inhalation of textile lint.

cough reflex; as a result, they are able to work their way deeply into the bronchial system. Patients who unwisely have acquired the habit of regularly ingesting moderate or even large amounts of such oil as a laxative are apt to aspirate part of the dose, and it is recognized that many of the low-grade, recurring pneumonias of past years were lipid pneumonias in the sense that they were triggered by smoldering infection about incompletely phagocytized oil droplets.

For at least 30 years the problem of aspirating lightweight oils has been recognized and the means of solving it known, but such information spreads slowly. Not many years ago in an institution at which the pathologists had done pioneer work on the lipid pneumonias, it was found that in at least one of its outpatient clinics prescriptions were still being written for "oily" nose drops. In addition to other disadvantages of the medicated ointments is the certainty that even when such ointments are placed in the nose of a patient who is up and about (to say nothing of the patient who goes to bed and to sleep) part of the ointment, liquefied by body temperature, will work its way into the lungs and cause trouble.

Figure 3 shows a large, approximately spheric lesion at the right cardiohepatic angle in a 56 year old man; this was discovered in a routine microfilm examination of the chest. There were no symptoms, and we assumed we were dealing with a neoplasm with associated pneumonia or atelectasis. The lesion was resected, and both the preoperative and postoperative diagnoses were neoplasm. Only after the specimen had been fixed, stained and sectioned was it found that there was no neoplasm at all; rather, it was a granuloma developing about a localized, chronic lipid pneumonia. With this information available, it was possible to obtain from the patient the admission that he had long been in the habit of ingesting a pint of mineral oil each week. Since the patient was a dealer in stock feeds, it is possible, although not established, that the inhalation of grain dust may have been a factor.[2]

Acute Chemical Pneumonia

An instance of an extremely severe pulmonary response to the inhalation of flocking compound intended for the decoration of Christmas trees was seen in a 31 year old woman. She had severe dyspnea soon after inhaling the material, and our film (figure 4, *top*), made 18 hours later, showed massive "infiltrates" in both lungs and acute enlargement of the heart. Treatment was directed at relief of anoxemia. Recovery was prompt, and five days later the lungs were clear and the heart was not enlarged (figure 4, *bottom*). On analysis, the spray was found to contain FREON®, methylene chloride, vinylene and stearic acid. The promptness with which the lesions cleared suggested that they were largely edema, although undoubtedly there was an underlying severe inflammatory reaction, so the diagnosis of pneumonia was justified in this case.

The widespread use of paints, lacquers, adhesives, moth repellents, etc., in spray cans adds a new hazard for those who must breathe the sophisticated air of the chemical age.

Inhalation of "Nontoxic" Dust and Lint

Although the vacuum cleaner has supplanted the dusty job of beating rugs at spring

house-cleaning time, central heating with oil, gas and electricity has relieved householders of the sooty, cough-inducing job of cleaning dozens of lengths of stovepipe before storing them for the summer, and most of our highways no longer stand ankle-deep in dust in dry weather, we seem to acquire new sources of atmospheric contamination about as rapidly as we eliminate the old ones. Some of these contaminants are, as we have seen, frankly toxic; however, it is indeed astonishing how well the human respiratory tract is able to keep most dusts out of the pulmonary alveoli and how well it tolerates a large number of those which do remain permanently or at least for long periods in the lung.

It will not be surprising if we learn eventually that the tolerance of the respiratory tract is not as complete as is now supposed, but certainly in comparison with silica, asbestos, beryllium, stearic acid, kerosene, etc., coal dust, the soot in our urban air, and many of the organic dusts and lints cause remarkably few symptoms in those who inhale them. Since these substances are highly radiolucent, we may be certain, however, that if their inhalation causes changes in chest x-rays it must be by virtue of lesions of some sort in the lung parenchyma which, in turn, cause local changes in the amount of air it contains. Figure 5 illustrates this point; it is the chest film of a 67 year old man whose occupation had long exposed him to an atmosphere containing large amounts of textile lint. He sought medical assistance because of moderate-grade but slowly increasing dyspnea; however, his symptoms were deceptively mild in view of the alarming appearance of his chest film. We assumed that the lesions were foreign-body reactions about particles of lint, and obviously the respiratory reserve must have been greatly reduced.

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The Editor's Mail

THE SUBCUTICULAR SUTURE

To the Editor:

The February 1961 issue of Postgraduate Medicine carried a very interesting article on subcuticular suture by Drs. Richard E. Straith, James M. Lawson and C. Jack Hipps. I enjoyed the article and thought it presented the management of facial lacerations very well. However, I do find that the authors, in order to emphasize their technic of the subcuticular suture, have been somewhat unfair in their blanket criticism of the use of interrupted sutures. The poor cosmetic results obtained with interrupted sutures in the cases illustrated are caused more by faulty initial technic than by choice of suture material.

I am sure that the authors do not wish to give the impression that the use of interrupted sutures will not produce excellent surgical results.

Bernard L. Morgan, M.D., *Jacksonville, Florida*

Dr. Morgan's letter was referred for comment to Dr. Straith, who has replied as follows:

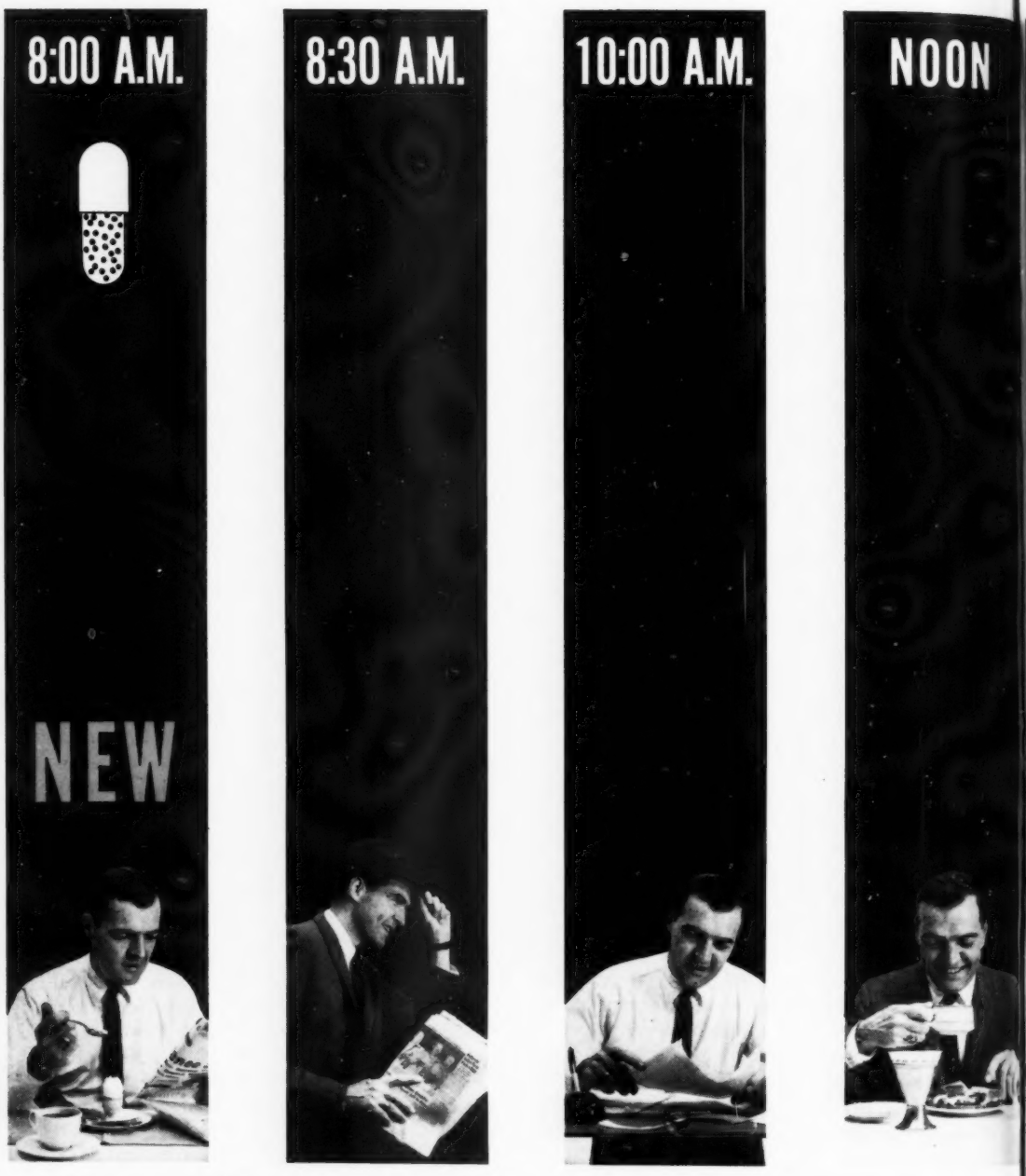
To the Editor:

In dealing with lacerations and scars of the face, the choice of wound closure used should be based on the percentage of good results. We know from experience that when only interrupted sutures are used, a considerably higher percentage of these cases result in suture marks and depressed, spread scars. This, as stated in our article, is due to a combination of scar tissue contracture and skin tension, which spreads the scar tissue. The only way we can increase our percentage of cosmetically perfect wound closures is by using a technic which will decrease the incidence of these complications.

The fact that the subcuticular suture technic has withstood the test of time (20 years at the Straith Clinic) and can be easily learned augurs well for its acceptance by those who are not satisfied with conspicuous scars and who are willing to practice enough to become proficient in its use.

The more completely such a technic is adopted by surgeons throughout the country, the higher the percentage of good results will be. This will reduce insurance settlements and jury awards, and, therefore, the cost to the public as a whole will be less.

Richard E. Straith, M.D., *Detroit*



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CAPSULES

Medicine from Abroad

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ENGLAND

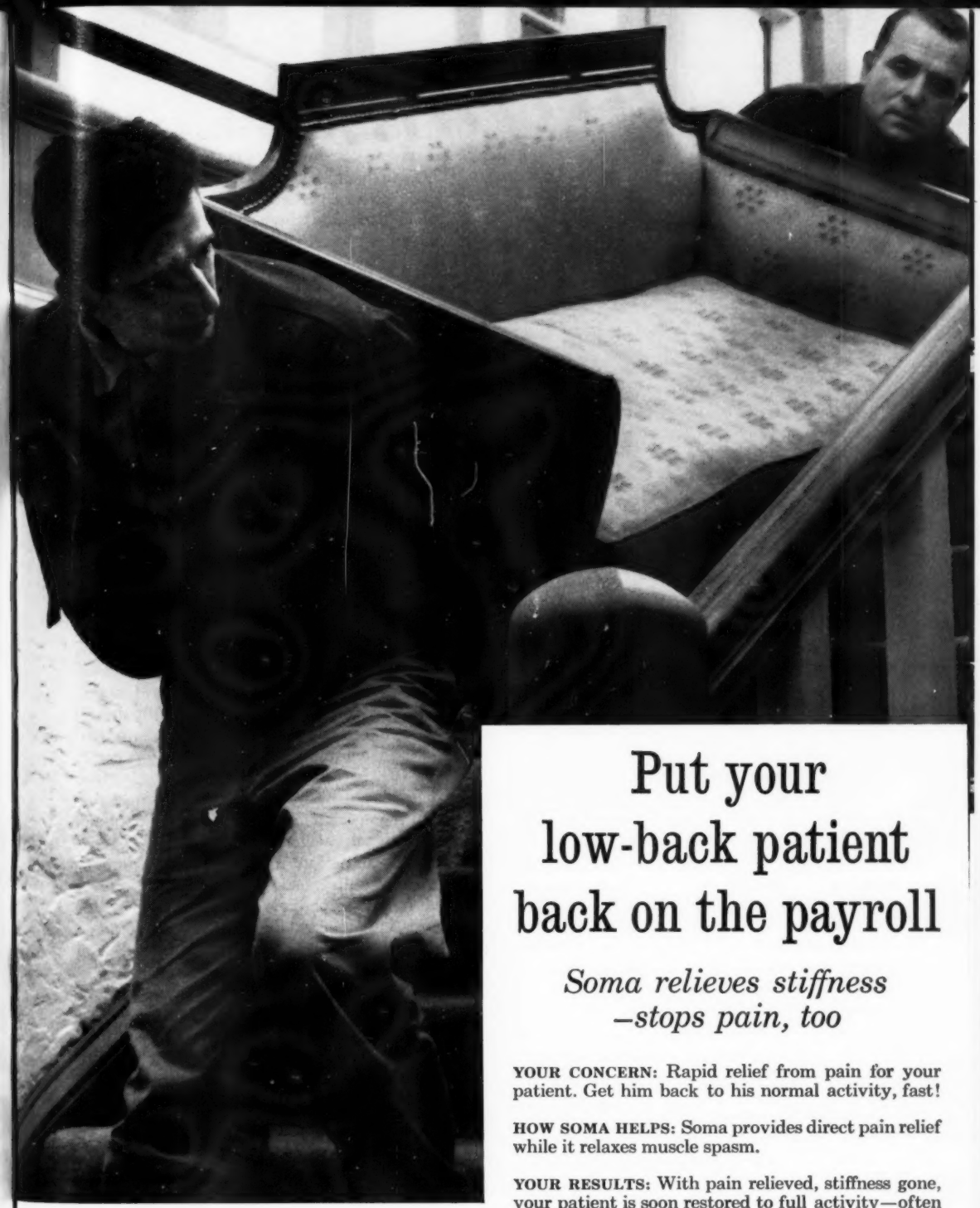
The value of thyroid extract—The potency of different batches of thyroid tablets has often been questioned, and the standards used for assaying them vary in different countries. During a discussion of this problem at the Fourth International Goiter Conference in London, it was stated that assays have shown that desiccated beef thyroid is only half as potent as pork thyroglobulin. Some brokerage firms have provided very cheap tablets which are only 20 per cent of the standard maintained by other drug houses and might rate at only 14 per cent on the goiter prevention test. In addition, seasonal changes can account for variations in the potency of thyroid. In preparing the tablets, calcium phosphate rather than lactose should be used as the diluent. It would be convenient to have only L-thyroxinsodium for prescription, since it is considered uniformly potent; whether it would remain so when stored is questionable.

In the *Lancet*, Dr. Alastair G. Macgregor, regius professor of therapeutics, University of Aberdeen Faculty of Medicine, Aberdeen, Scotland, asked a very pertinent question: "Why does anybody use thyroid B.P.?" He said that there was ample evidence in favor of more extensive use of a refined and pure therapeutic product. Biologic assay of thyroid tablets and the dating of batches of thyroid tablets would become unnecessary if all physicians used thyroxin. There is ample pharmacologic, therapeutic and economic justification for recommending that thyroxin be used for all thyroid replacement therapy to the exclusion of preparations of dried thyroid.

Causes of peptic ulcer—In a symposium in the *Practitioner*, Dr. Mervyn Susser, University of Manchester Faculty of Medicine, Manchester, reviewed the influence of environmental factors on the incidence of peptic ulcer. He said that particular occupations have long been thought to carry a special risk of peptic ulcer, but Doll, Jones and Buckatzsch found no basis for this belief. This team provided well-founded knowledge on the association of ulcer and occupations from a survey of ulcer morbidity in London. Agricultural workers had a low ulcer morbidity, which conforms with their low mortality and with observations made in most other studies. The high morbidity recorded for doctors could be ascribed, at least in part, to early and accurate diagnosis. Managers and foremen in industry showed a modest excess of duodenal ulcers.

Marked differences in the occurrence of peptic ulcer are found at different ages and between the sexes, and these differences have altered over the last 150 years. In the 1950s there were signs that the incidence of both gastric and duodenal ulcers had reached a plateau and had begun to diminish, especially in younger age groups. It

(Continued on page A-82)



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> Kestler reports in controlled study: *Average time for restoring patients to full activity: with Soma, 11.5 days; without Soma, 41 days.* (*J.A.M.A. Vol. 172, No. 18, April 30, 1960.*)

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seems probable that the incidence of peptic ulcers which early this century began to affect young and then middle-aged men is receding in these age groups because they have experienced environments different from those of their predecessors. Specific factors which may be concerned in the variable occurrence of peptic ulcer in different environments include diet, smoking, anxiety from external stress, and personality stress.

U. S. S. R.

All-Union Rheumatological Conference—At a meeting of the All-Union Rheumatological Conference in Moscow, reports were given on the morphogenesis and immunogenesis of Sokolsky-Bouillaud disease, the diagnosis of rheumatic carditis and evaluation of activity of the rheumatic process, and the treatment of rheumatism.

According to A. I. Strukov, Moscow, the antigens of hemolytic streptococci and the autoantigens play an important role in the development and clinicomorphologic manifestations of Sokolsky-Bouillaud disease. He assumes that the accumulation of plasma cells with pyroninophilic protoplasm in the foci of inflammation is a manifestation of the immunologic changes that occur in the organism in this disease. The plasma-cell reaction also occurs in the interparoxysmal period of the disease, a fact which indirectly may confirm the assumption that the rheumatic process is continuous.

N. N. Gritsman and A. A. Rogov, Moscow, failed to find any direct relation between the presence of Aschoff-Talalayev granulomas, seen on biopsy of the auricles of the left atrium, and the clinical activity of rheumatic fever. A. A. Tustanovsky and G. V. Orlovskaya, Moscow, pointed out that sclerosis occurs in rheumatic carditis as a result of disorganization of mature structures ("primary" sclerosis, according to Talalayev) and as a result of cellular proliferation. In this connection, the activity of fibrinogenic cells causes the formation of collagen in specific foci.

V. K. Beletsky, Ryazan, stated that rheumatic fever is characterized by development of the primary Graeff-Klinge symptom, with the infectious process spreading lymphatically toward the heart (with the development of tonsillitis, lymphadenitis and carditis), and by early general toxic and allergic reactions.

According to the data presented by V. V. Mikheev, Moscow, lesions of the cerebral vessels in rheumatic fever should not be considered as complications but rather as part of the syndrome.

Raska, Rott and Bednar, Czechoslovakia, and other participants discussed the etiologic and pathogenic roles of streptococcal infection, while V. I. Ioffe spoke of the role of modern clinical immunology in the study of rheumatic fever. V. D. Timakov and G. Y. Kogan, Moscow, stressed the pathogenic significance of the group L hemolytic streptococci in rheumatic conditions. Presentations by A. Robecchi, Turin, W. Graham, Toronto, and P. P. Sakharova and associates also acknowledged the pathogenic effect of streptococcal infection on rheumatic fever.

G. D. Zalessky and N. N. Vorob'eva, Novosibirsk, reported on studies on the isolation of virus R from rheumatic patients. However, the role of this virus in the development of rheumatic fever has not yet been proved.

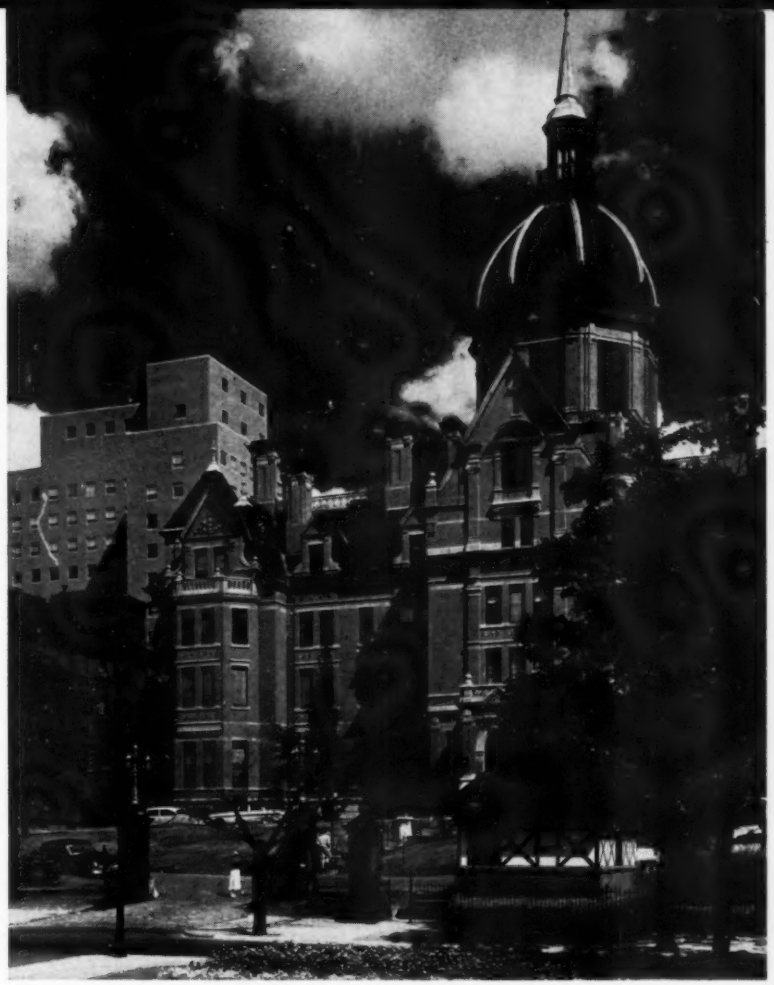
Several speakers, including N. Svartz, Stockholm, F. Coste, Paris, Kellgren, Manchester, England, and P. P. Kaznacheev, Novosibirsk, discussed the concept of rheumatoid arthritis and rheumatic fever as diseases connected with autoimmune reactions and impairment of protein-enzymatic metabolism. Hans Selye, Montreal, emphasized the role of stress in the function of neurohormonal mechanisms as the most important pathogenic link in the rheumatic chain. Philip Hench, Rochester, Minnesota, described the part played by impairment of cortisone balance in the development of collagen diseases and particularly of rheumatoid arthritis.

A. I. Nesterov and V. I. Skachkov, Moscow, reported on a diagnostic test for rheumatic fever based on electrophoretic determination of the increase in gamma-globulin when the gamma-globulin from a patient's serum is fused with that of antiserum prepared by immunizing rabbits with gamma-globulin from patients who have rheumatic disease. E. M. Tareev, Moscow, stressed the importance of distinguishing between rheumatic carditis and cardiac lesions in other collagen diseases.

Modern treatment of rheumatic fever, with skillful use of both old and new antirheumatic remedies, ensures more satisfactory immediate and long-lasting results than were possible with the treatment used 10 to 15 years ago. Kriegel of Czechoslovakia and others pointed out the effectiveness of systematic control of the streptococcal infection and allergic reactivity in preventing relapses of rheumatic fever.

Postgraduate Medicine

SPECIAL ISSUE



The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital

JAMES P. ISAACS, M.D.
Guest Editor

MAY 1961

MILTON S. EISENHOWER

FOREWORD

THE Johns Hopkins medical community is once again honored to present the results of staff research ranging across a broad spectrum of the medical sciences in this special issue of POSTGRADUATE MEDICINE.

These contributions by Johns Hopkins clinicians provide strong evidence of the continuing commitment of the Hopkins Medical Institutions to bring the results of laboratory research to the patient's bedside in the unceasing battle against disease.

An intimate relationship between medical teaching and research and clinical practice has always been the guiding principle of the Hospital and the School of Medicine. The general validity of this concept can, I think, be measured by the fact that today it forms the basis of all high-quality medical education.

It is perhaps trite but nonetheless true that never has so much been expected by so many from the American medical profession. There are demands for both quantity and quality in the training of physicians, for the widest application of the latest advances in medical research, and for the initiation of health programs in the underdeveloped regions of our planet. These insistent expectations pose critical problems. If the needs of our own and future generations are to be met, we must look to postgraduate medical education to play a crucial and a demanding role.

MILTON S. EISENHOWER
President, The Johns Hopkins University

Coronary Thromboendarterectomy for Angina Pectoris

DAVID C. SABISTON, JR. AND ALFRED BLALOCK*

The Johns Hopkins University School of Medicine, Baltimore

Total occlusion of one or more major *coronary arteries by atherosclerosis is characteristically found in the majority of patients with the clinical manifestations of severe angina pectoris.*

Sites of arterial obstruction in patients with severe angina pectoris may be localized precisely by coronary arteriography, and in selected cases it is possible to perform thromboendarterectomy under direct vision. The findings in a group of patients treated in this manner are presented and discussed. Results after a limited period of observation appear sufficiently encouraging to recommend this approach in the management of selected patients with intractable angina pectoris.

CORONARY atherosclerosis with arterial occlusion is the underlying pathologic basis for the vast majority of cases of angina pectoris. In an extensive clinical and pathologic study, Blumgart, Schlesinger and Davis[1] concluded that every patient suffering primarily from angina pectoris without evidence of valvular disease or arterial hypertension has complete occlusion of one or more *major* coronary arteries. This finding has been confirmed by others and is now accepted as a characteristic feature of the disorder. Under these circumstances, occlusion of a major coronary artery is followed by reduction of the flow of blood to a part of the myocardium, and symptoms of ischemia appear. This condition is basically similar to the symptom complex associated with atherosclerotic arterial occlusion of vessels of the lower extremity in which claudication is a frequent complaint. In the recent past it has been shown that direct removal of obstructing lesions in such cases often produces relief of symptoms. It is perhaps logical to assume that the removal of similar lesions from the coronary arteries might be a rational method of therapy for patients with angina pectoris.

Thromboendarterectomy has been employed successfully on large arteries such as the aorta and the iliac and femoral arteries, and more

*Department of Surgery, The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital, Baltimore, Maryland.

This work was aided by a grant (H-2864) from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service, Bethesda, Maryland.

DAVID C. SABISTON, JR.

ALFRED BLALOCK

recently smaller vessels including the subclavian, vertebral and superior mesenteric arteries have been attacked, with encouraging results. Several observers have suggested the use of this method in patients with coronary occlusion, and the first successful attempt was reported by Bailey and associates[2] in 1957. Shortly thereafter, Longmire, Cannon and Kattus[3] described an improved method for the performance of this procedure and reported successful results. In our laboratory a group of perfusion and pathologic studies on hearts of patients with angina pectoris obtained at the time of postmortem examination indicated this approach to be both rational and technically feasible.[4] Recently an initial clinical study employing this method has been reported.[5]

Pathologic Features of Coronary Atherosclerosis

Coronary atherosclerosis is a progressive disease, and the earliest microscopic changes characteristic of the condition have been described in the newborn infant. These lesions consist of rupture, degeneration and regeneration of the internal elastic membrane together with deposits of mucopolysaccharide and proliferation of endothelial cells and fibroblasts.[6] Gross lesions subsequently appear in the form of small yellow deposits of lipoid material visible beneath the intima, and have been described as being present in one-half the hearts examined at autopsy during the second decade of life.[7] With the passage of time these "lipoid streaks" become covered with hyalinelike connective tissue and form rounded or irregular plaques which project into the arterial lumen. It is possible that this stage of the disease is actually the result of small intravascular thrombi which form on the fatty deposits and subsequently become organized.[8] In any event it is certain that *secondary* thrombosis and calcification may occur either on or within these fibrous plaques, particularly at sites of luminal narrowing. Severe forms of these lesions may appear early in life, and this has been emphasized by French and Dock[9] in their review of the pathologic findings in 80 *fatal* cases of coronary atherosclerosis in young soldiers during World War II.

The distribution of atheromas in the coronary arterial tree is an important aspect of this problem and has received considerable attention. Several studies recording the localization and degree of coronary lesions have shown that in nearly every decade of life the severity of atherosclerosis is greatest in the anterior descending coronary artery, followed in order of incidence by the right main coronary artery, the left circumflex, the left main, the right posterior descending, and the right marginal arteries.[10,11] Furthermore, the severity of the changes is almost invariably greatest in the proximal third of the vessel. Schlesinger and Zoll[12] conducted a thorough gross and microscopic study of 400 hearts at the time of postmortem examination and concluded: "Most zones of occlusion of coronary arteries are less than 5 mm. in length." They further observed: "The majority of coronary occlusions are found within 3 cm. of the mouth of these vessels." It is their view, and one that is documented clearly by their pathologic observations, that angina pectoris occurs only in the presence of total occlusion of one or more of the major coronary arteries.

One of the features of coronary atherosclerosis which is of particular importance in relation to revascularization procedures is the status of the arterial bed *distal* to the site of occlusion. Coronary injection studies have shown that intercoronary anastomoses greater than 40 μ in diameter are not found in the normal human heart. However, in the presence of arterial occlusion, collateral vessels measuring 40 to 200 μ in diameter have been demonstrated consistently.[1] It is these vessels which

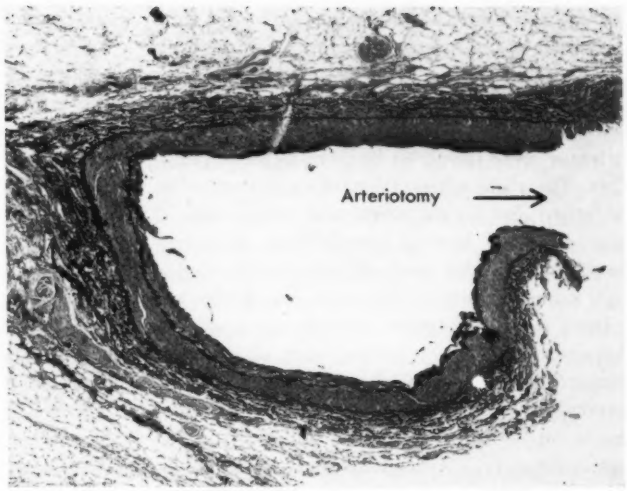


FIGURE 1. Photomicrograph of the right main coronary artery at its origin from the aorta after thromboendarterectomy. Section taken at postmortem examination from the heart of a victim of myocardial infarction following total occlusion of the right coronary artery. The thrombus in the right coronary artery was removed through the arteriotomy incision which is shown. The internal and external elastic layers are clearly seen, demonstrating that the occluding lesion primarily involved the intimal layer (Verhoeff-Van Gieson).

supply blood to the myocardium at points distal to a site of occlusion. Further, it can be shown that thromboendarterectomy may be performed in hearts with localized coronary atherosclerosis leaving an arterial lumen with a smooth intravascular surface (figure 1). Following removal of the thrombus, a marked increase occurs in the amount of fluid which can be perfused through the previously obstructed coronary artery.[4] These observations, in conjunction with the histologic findings, support the view that coronary arteries distal to an obstruction are often patent. This is important from the *physiologic* point of view, and Gregg and associates[13,14] have performed some significant experiments which shed light on the hemodynamics of coronary occlusion. In their studies, major coronary arteries were occluded and determinations of back pressure and backflow were made at varying intervals. Collateral channels developed with the passage of time and conducted appreciable quantities of blood, as demonstrated by a marked increase in the backflow and back pressure in the distal coronary arteries. These observations are important in a consideration of the rationale of myocardial revascularization.

Case Reports

Case 1—A 41 year old engineer was admitted to The Johns Hopkins Hospital with severe angina pectoris. The family history was positive in that the father had angina pectoris and died following a cerebrovascular occlusion. The patient's past history was not contributory. The present illness began seven years prior to admission with the sudden onset of severe chest pain. An electrocardiogram was interpreted as showing evidence of myocardial infarction. He was treated in another hospital with bed rest for two months and was discharged asymptomatic. Two years later the onset of chest pain with mild exertion was first noticed. This gradually became more severe. The pain could be induced by walking 50 ft. and was partially relieved by sublingual nitroglycerin. Within a short period the symptoms became increasingly severe and he was forced to cease work.

The physical examination was essentially unremarkable. Blood pressure was 120/80 mm. Hg, and all peripheral pulses were palpable. The serum cholesterol concentration was 290 mg. per cent. The electrocardiographic tracing at rest was interpreted as normal, but following exercise ventricular extrasystoles appeared with marked depression of the S-T segment in leads I, II, III and V_4. These findings were interpreted as evidence of myocardial ischemia. A coronary arteriogram was made, and the left coronary artery and its branches filled normally; the right coronary

artery was visualized for a distance of 1 cm., at which point it was occluded.

On February 12, 1959, a bilateral anterior thoracotomy was performed. The left main, anterior descending, and circumflex coronary arteries were found to be firm but compressible. The right coronary artery was somewhat enlarged and on palpation was quite hard. It was dissected free of surrounding structures and was occluded with an arterial clamp for five minutes. During this time no change occurred in the systemic arterial pressure, the appearance or action of the heart, or the electrocardiogram. It was felt that the coronary artery was totally occluded. An incision was made on its anterior surface and a thrombus approximately 7 cm. in length was removed. This was followed by vigorous proximal and distal flow, and the arteriotomy was closed. The patient recovered uneventfully. The postoperative electrocardiogram was interpreted as showing less evidence of ischemia. The patient occasionally has chest discomfort but is symptomatically considerably improved and has returned to work.

Case 2—A 49 year old foundry worker was referred with a diagnosis of angina pectoris. Two years previously he had noted the onset of substernal pain which was characteristically relieved by sublingual nitroglycerin. An electrocardiogram showed evidence of myocardial ischemia following exercise. The chest discomfort became progressively severe and he was forced to cease work despite maintenance on a medical regimen.

Physical findings were not remarkable. Blood pressure was 140/80 mm. Hg. All arterial pulsations were present but were diminished in the lower extremities. The serum cholesterol concentration was 365 mg. per cent. The electrocardiogram showed depression of the S-T segment following exercise and was considered indicative of myocardial ischemia. A coronary arteriogram demonstrated satisfactory visualization of the left coronary artery and its branches but no filling of the right coronary artery.

A median sternotomy was performed on May 14, 1959. Palpation of the left coronary artery and its branches revealed that they were thickened but compressible. The right coronary artery was hard, and total occlusion of this vessel for five minutes did not affect the arterial pressure, heart action, or electrocardiogram. The right coronary artery was opened, and a thrombus 5 cm. in length was removed. Good proximal and distal bleeding was obtained. Microscopic examination of the specimen showed total occlusion of the lumen at one point and a lumen of varying size in the remainder of the thrombus. The patient's postoperative course was unremarkable. The electrocardiogram at rest was normal, but after exercise it continued to show depression of the S-T segment. Since discharge from the hospital, the patient has noted a marked reduction in the anginal pain compared with his preoperative condition and has resumed work.

Case 3—A 43 year old salesman was admitted with angina pectoris. Fifteen months previously he first experienced an episode of substernal pain. His physician obtained an electrocardiogram which was interpreted as showing evidence of myocardial ischemia. Nitroglycerin was prescribed and was found to relieve the pain. The attacks became more frequent, and in April 1958 ligation of both internal mammary arteries was performed at another hospital. This did not afford relief, and ultimately large amounts of nitroglycerin became necessary in an attempt to control the pain. The patient was forced to retire completely from work, and at the time of admission he could induce an attack of angina by walking the length of a room.

Physical examination was essentially negative. Blood pressure was 125/70 mm. Hg. The serum cholesterol concentration was 175 mg. per cent. An electrocardiogram showed T wave changes indicative of coronary arterial insufficiency. A coronary arteriogram demonstrated an occlusion in the left main coronary artery. The right coronary artery was well demonstrated, but a stenosis was present at its origin.

On September 11, 1959, a posterolateral thoracotomy was performed. The left main coronary artery was quite hard, and occlusion of the vessel did not produce any change in the arterial pressure or the electrocardiogram. The vessel was opened, and a thrombus which

totally occluded the left main and circumflex coronary arteries was removed. The patient tolerated the operative procedure well but later the same day irreversible ventricular fibrillation developed. Postmortem examination revealed residual plaques and fresh thrombus in the left coronary artery. The right coronary artery showed atherosclerosis with a short area of stenosis at its origin.

Case 4—A 41 year old man was admitted with a history of severe angina pectoris which ultimately required him to cease work despite maintenance on a medical regimen. Physical examination was not remarkable except for the presence of an aortic systolic murmur. The electrocardiogram following exercise was interpreted as showing minimal evidence of myocardial ischemia. A coronary arteriogram demonstrated satisfactory filling of the left coronary artery and its branches and occlusion of the right coronary artery.

On February 4, 1960, a median sternotomy was performed and the right coronary artery was exposed. Palpation revealed the vessel to be quite sclerotic and not compressible. Total occlusion of the vessel did not produce any change in the arterial pressure or in the electrocardiogram. The artery was opened, and a thrombus approximately 7 cm. in length was removed. This was followed by good proximal and distal flow. Microscopic examination of the specimen revealed "severe luminal narrowing due to fibro-fatty atherosclerosis with intraluminal fresh and organizing thrombus." The patient made a rapid recovery. When last examined four months following operation, he no longer required nitroglycerin and had returned to work. A ballistocardiogram showed improvement, and the electrocardiogram after exercise was normal.

Case 5—A 47 year old chemical engineer was referred with a diagnosis of angina pectoris. The family history was positive in that the father and a brother died with coronary disease. The patient's present illness began seven years previously, with the onset of substernal pain radiating into the left shoulder and arm. A diagnosis of angina pectoris was made and a medical regimen was instituted. The anginal pain became increasingly severe, and nitroglycerin no longer afforded relief. At the time of admission to the hospital the patient could induce an attack by walking only one block.

Physical examination was not remarkable. Blood pressure was 135/90 mm. Hg, and all peripheral pulses were present and equal. The electrocardiogram showed marked evidence of myocardial ischemia after exercise. A coronary arteriogram demonstrated filling of the left coronary artery and its branches but total occlusion of the right coronary artery.

On February 26, 1960, a median sternotomy was performed. The right coronary artery was palpated and found to be markedly sclerotic. Occlusion of the vessel at its origin with an arterial clamp did not affect the heart. The vessel was opened and found to contain an organized thrombus. Good proximal and distal bleeding followed removal of the thrombus. Microscopic examination of the specimen showed "severe luminal narrowing due to fibro-fatty atherosclerosis with luminal occlusion in the proximal portion of the specimen and fresh and organized thrombus with recanalization in the distal specimen." The postoperative course was unremarkable. Since discharge, the patient has improved steadily and has returned to full-time work without symptoms of angina.

Case 6—A 45 year old merchant was admitted with the complaint of marked substernal pain following exercise. The present illness had been long, and there were a variety of examinations prior to the establishment of a definitive diagnosis. He was first admitted in 1957, and there were three subsequent admissions, ultimately culminating in an electrocardiogram which showed marked evidence of myocardial ischemia following exercise. A medical regimen was tried but did not produce relief. A coronary arteriogram demonstrated total occlusion of the right coronary artery with normal filling of the left coronary artery and its branches.

On May 18, 1960, a median sternotomy was performed and the right coronary artery was exposed. It was quite firm, and total occlusion of the vessel did not affect the blood pressure or the electrocardiogram. The left

FIGURE 2. Median sternotomy, illustrating exposure of the right coronary artery. The pericardium is opened and the right coronary artery is being dissected. This approach provides excellent exposure of this vessel.

coronary artery was not remarkable. The right coronary artery was opened, and a thrombus 5 cm. in length was excised. Following its removal, excellent proximal and distal flow was obtained. The microscopic examination of the vessel demonstrated a "severe luminal occlusion due to fibro-fatty atherosclerosis with patent distal lumen." The patient recovered uneventfully. Four months later the electrocardiogram showed an improvement in the T waves, and the patient could walk an unlimited distance without anginal pain.

Selection of Patients and Operative Technic

Each of the six patients described was selected for operation as a result of *intractable* angina pectoris. Each patient had been investigated thoroughly and a medical regimen had been tried without significant relief. All the patients had to cease work, and in some instances could walk only a short distance without the onset of severe angina. Another feature common to this group was the absence of demonstrable evidence of myocardial infarction. One of the patients (case 1) probably had a minimal infarction with the original episode of angina, but there was no subsequent evidence to substantiate this on the electrocardiogram or at the time of direct examination during the operation.

In addition to a typical history of characteristic angina pectoris, five of the six patients had changes in the electrocardiogram interpreted as evidence of ischemia. Of particular importance in the objective preoperative eval-

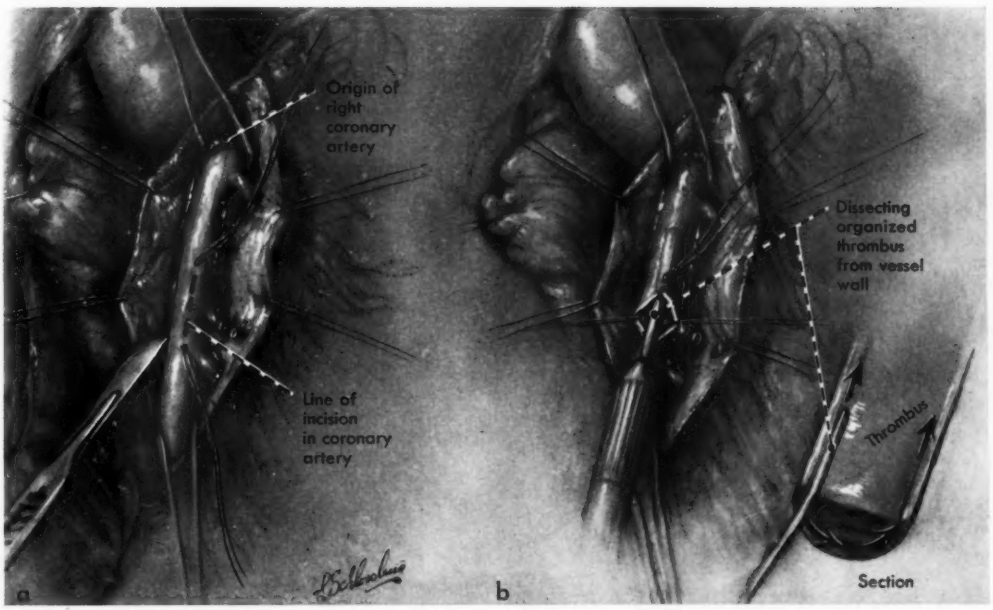


FIGURE 3. a. Illustration of the right main coronary artery following dissection. The dotted line indicates site of arteriotomy.

b. An incision is made on the anterior surface of the artery and a dissector is employed to separate the thrombus from the arterial wall. In the lower right, a group of arrows indicate the direction in which the arterial dissector is passed in order to establish a plane of cleavage.

uation in *every* case was the demonstration of occlusion of a *major* coronary artery in the arteriogram. A total block of one of the large vessels was found in each instance. Furthermore, in all but one case (case 3) the other *major* coronary vessels were found to have satisfactory lumens. Therefore, it was possible to demonstrate the site of occlusion with reasonable accuracy prior to operation. It should be emphasized that coronary arteriography is now an established procedure with little risk when performed properly. In our experience this examination has been employed in more than 50 cases without significant morbidity and with no mortality.[15] Recently the use of cinearteriography has increased the value of roentgenographic evaluation.

For the operative procedure, anesthesia is induced with PENTOTHAL® and maintained with nitrous oxide along with small amounts of intravenous DEMEROL®. Adequate ventilation with oxygen is essential. The thoracotomy is made in accordance with the site of arterial occlusion. For the right coronary artery a median sternotomy is performed and provides excellent exposure (figure 2). The left coronary artery, including its anterior descending and circumflex branches, may be exposed satisfactorily through a left posterolateral approach. The pericardium is opened and the occluded coronary artery is exposed (figure 3). The vessel is dissected at its origin from the aorta and is totally occluded with an arterial clamp for five minutes. The electrocardiogram is monitored continuously. If occlusion of the vessel does not produce a change in the tracing or in the arterial pressure, it may be assumed that little blood is being conducted through the vessel at that site. The artery then may be occluded safely for several minutes while an arteriotomy and thromboendarterectomy are performed.

The method which we have employed is essentially that of Longmire and associates.[3]

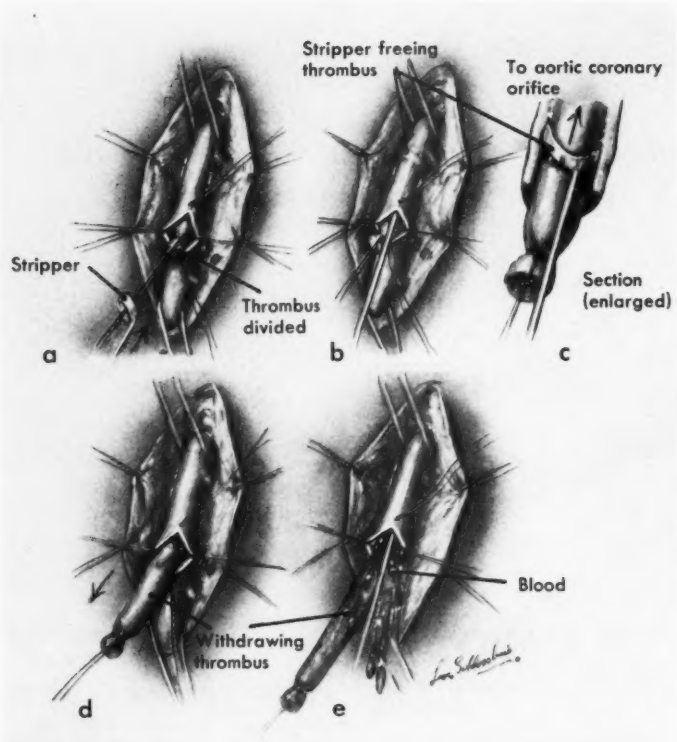


FIGURE 4. a. The thrombus has been divided between ligatures.

b. The ligature is passed through the orifice of the coronary stripper and the latter is advanced toward the aorta, freeing the thrombus from the arterial wall.

c. Enlarged illustration of coronary stripper employed for separation of the thrombus from the arterial wall.

d. Traction is applied to the ligature with removal of the thrombus after complete separation.

e. With removal of the proximal thrombus a strong jet of blood suddenly escapes from the artery. (The arterial dissector and endarterectomy loops are those designed by Longmire and Cannon.[3])

A coronary dissector is used to obtain a cleavage plane between the thrombus and the arterial wall. Following separation from the arterial wall at the site of the arteriotomy, the thrombus is doubly ligated and divided between ligatures (figure 4). The ligature is then passed through the stripper which is advanced to separate the thrombus until it is completely free and may be removed (figure 4). At this time a strong proximal flow should be present. An arterial occlusion clamp is placed on the proximal artery, and the distal thrombus is removed in a similar manner. After good backflow is obtained, the arteriotomy is closed carefully with 7-0 arterial silk (figure 5). It is impressive how easily the cleavage plane in the arterial wall may be established. This is undoubtedly aided by the fact that coronary arteries severely involved with atherosclerosis often are larger than normal.

For the first patients in this group, cardiopulmonary bypass was prepared at the time of endarterectomy and maintained ready for use if indicated. However, total occlusion of the involved vessels was tolerated without event and it was not necessary to employ extracorporeal circulation. In instances of severe coronary atherosclerosis with multiple sites of occlusion, cardiopulmonary bypass may be required and perhaps is mandatory. If multiple involvement of major coronary arteries is present, this should be recognized on the coronary arteriograms and should provide an indication that the pump-oxygenator is needed. In the future it is likely that coronary thromboendarterectomy will be aided by a combination of extracorporeal circulation and deep hypothermia with cardiac arrest. Although the beating heart has not been a significant handicap in the performance of thromboendarterectomy in the present group, with the extension of the technic to include more severe forms of the disease involving smaller vessels the quiet heart would offer a definite advantage.

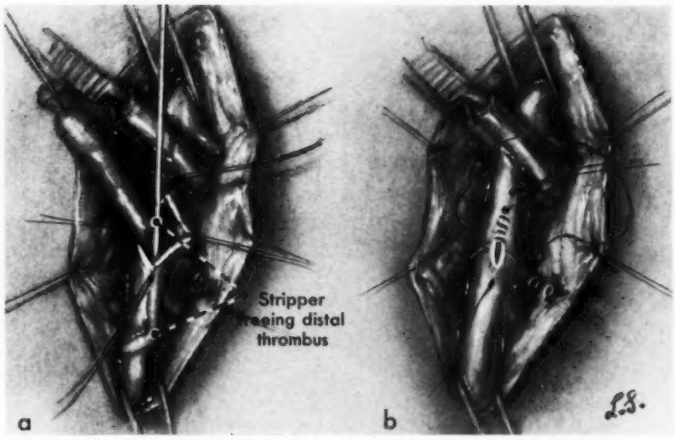


FIGURE 5. a. An arterial stripper is applied to the distal thrombus with careful removal of the entire lesion. During this time the proximal artery is occluded with an arterial clamp.

b. The arteriotomy is closed carefully with 7-0 silk.

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Discussion

Coronary atherosclerosis represents one of the most important of the unsolved problems in clinical medicine, and this fact is clearly emphasized by vital statistics of this country and of others, which indicate that its incidence as a cause of death is increasing annually. In the past, a variety of surgical procedures have been advocated for the relief of myocardial ischemia, particularly when severe angina pectoris was a prominent feature of the disease. Despite the enthusiasm of several groups interested in the surgical aspects of this problem, it is apparent that the majority do not regard the currently available revascularization technics with favor. This reasonable attitude is due in large part to the fact that the results of such operations often are equivocal and difficult to evaluate objectively.

In recent years, DeBakey and others have introduced a more vigorous attitude toward the general problem of arterial occlusion in a variety of disease states and have applied a more direct therapeutic approach.[16,17] Thromboendarterectomy of the aorta and iliac vessels for vascular obstruction has been firmly established, and more recently this procedure has been employed on smaller vessels including the internal carotid, vertebral and superior mesenteric arteries.[17-19] Following the report by Bailey and associates[2] of successful coronary endarterectomy in 1957, Longmire and co-workers[3,20] described an improved technical approach to this problem with encouraging results in a group of patients with angina pectoris.

The rationale of direct thromboendarterectomy for coronary arterial occlusion is dependent on several basic factors which include (1) the anatomic distribution of the lesions of coronary atherosclerosis, (2) the status of the arterial bed distal to the sites of occlusion, (3) the technical feasibility of coronary en-

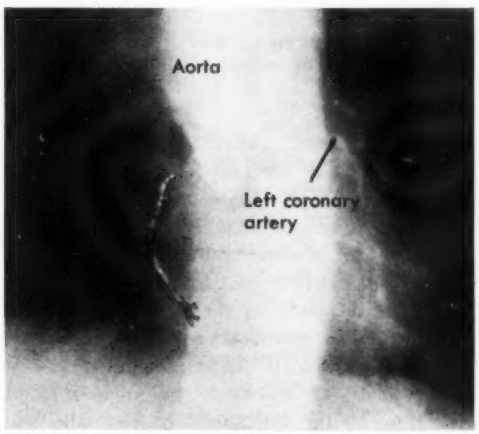

FIGURE 6. Coronary arteriogram of patient with right coronary occlusion (case 5). The origin of the left coronary artery with its anterior descending and circumflex branch is seen. The specimen removed from the right coronary artery at the time of operation is superimposed on the chest roentgenogram in its anatomic position.

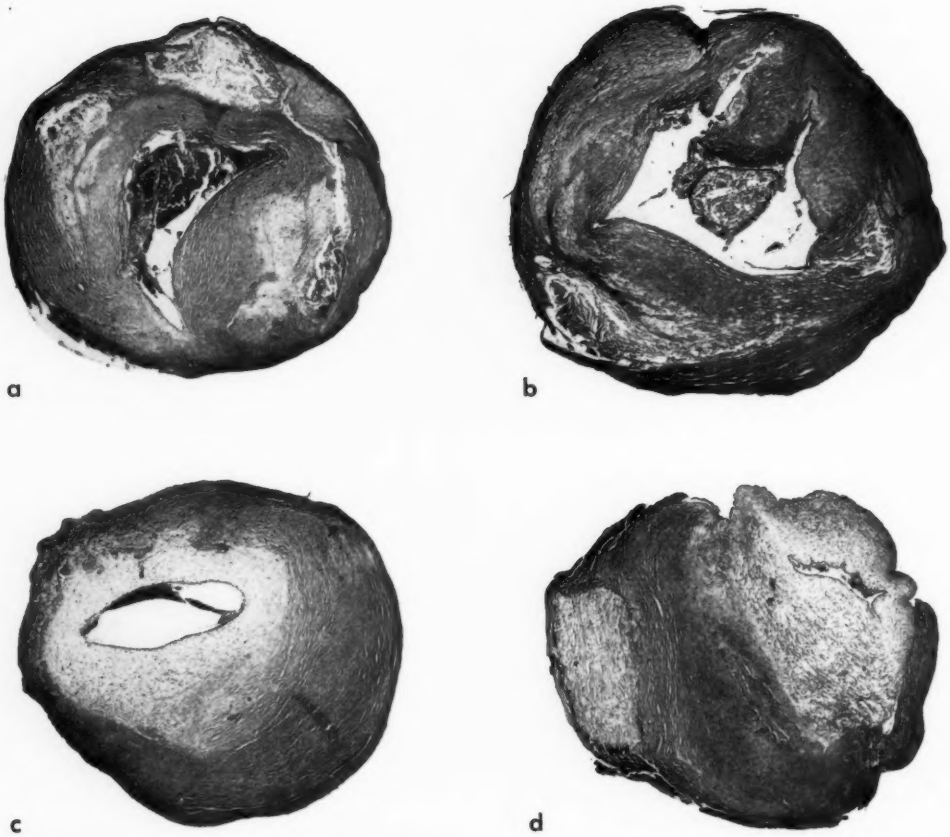

FIGURE 7. Serial photomicrographs of the thromboendarterectomy specimen removed in case 4. The presence of a lumen is seen in some sections, with total occlusion in d.

darterectomy, and (4) the predisposition of small arteries to thrombosis following direct operation. Although there can be little doubt that atherosclerosis may involve the entire coronary tree, a number of careful observers have emphasized the fact that this disease frequently is localized to the proximal portions of the larger coronary vessels.[1,10,12,21,22] Schlesinger and Zoll[12] have concluded that in the majority of instances the sites of *total* occlusion in the coronary arteries are less than 5 mm. long and that such sites are often within the proximal 3 cm. of the origin of these vessels. It is of prime importance that the arterial bed distal to the obstruction be patent if thromboendarterectomy is to be successful. The careful injection studies of Blumgart and associates[1,23] showed that large collateral vessels are characteristically present in association with occluding lesions in the coronary arteries. In our own experience, studies on the direct perfusion of coronary arteries in the hearts of victims of coronary occlusion show a marked increase in the volume of flow through such vessels following removal of occluding lesions.[4]

The technical feasibility of coronary endarterectomy can be demonstrated on hearts obtained at postmortem examination. Microscopic sections of the vessel wall after thromboendarterectomy show a smooth internal surface and stress the fact that atherosclerosis

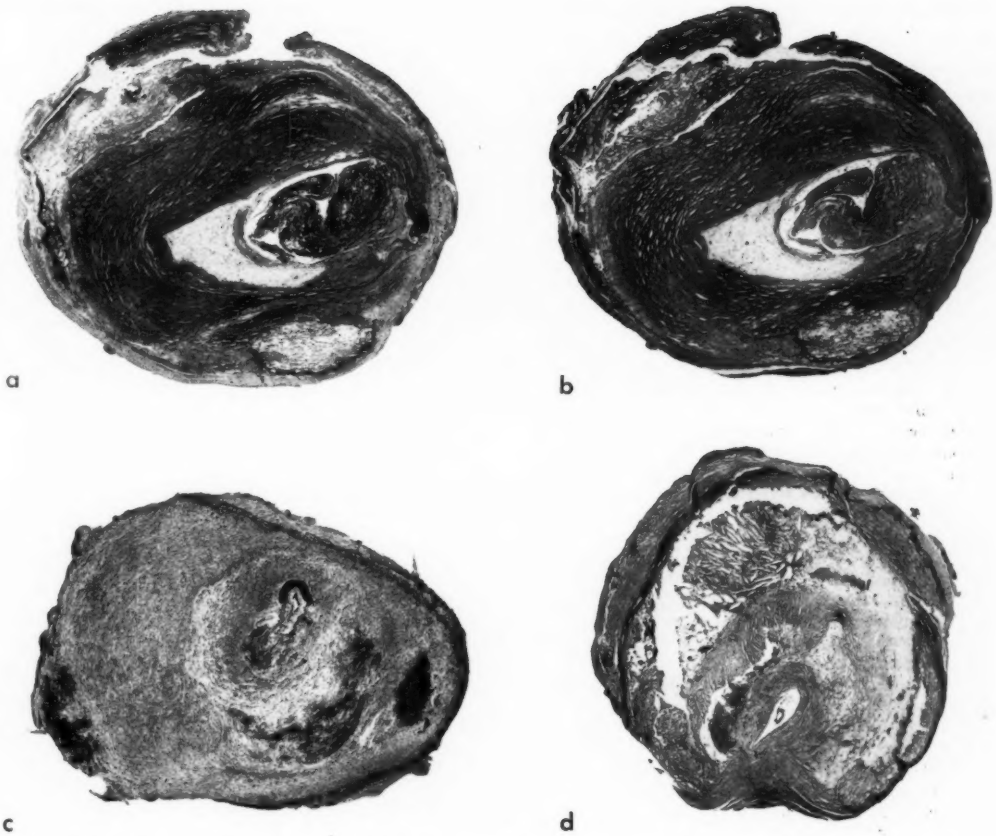

FIGURE 8. Serial photomicrographs of thromboendarterectomy specimen removed in case 5. In some areas the thrombosis is complete, and in others a small lumen is present.

primarily involves the *intimal* layer of the vessel (figure 1).

Finally, the predisposition of the coronary vessels to thrombosis following endarterectomy is as yet an undetermined factor but one which has been given study.[24] In our laboratory, small vessels such as the femoral arteries of the dog withstand intimectomy without the development of thrombosis in a high percentage of experiments.[25] Furthermore, this procedure may be performed in the presence of experimental hypercholesteremia and atherosclerosis and is followed by long-term patency of the lumen in about half such vessels.[26]

In the present clinical study, six patients with severe angina pectoris are presented. The cases were characterized by a typical clinical history and by electrocardiographic evidence of myocardial ischemia. Coronary arteriograms demonstrated an occlusion of a *major* coronary artery in each case (figure 6). Thromboendarterectomy was performed in all six cases, and the findings at operation and the microscopic appearance of the thrombi confirmed the preoperative diagnosis (figures 7 and 8). The clinical response in these patients during a brief period of observation has been encouraging. It appears reasonable to believe that this method should be employed in *selected* cases of severe angina pectoris due to coronary atherosclerosis, particularly in instances in which other methods of therapy fail

to afford relief. The multiple problems known to be associated with the evaluation of any treatment for this complex disorder are fully recognized. Although the initial results appear encouraging, there is little doubt that additional cases and an extended period of observation will be necessary before definite conclusions may be drawn regarding the ultimate role and efficacy of this procedure.

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Staphylococcal Pneumonia in Childhood

CLINICAL OBSERVATIONS IN 67 CASES

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Factors in diagnosis and management of staphylococcal pneumonia in childhood are discussed, based on observations in 67 cases over a four year period.

Early suspicion of this entity and prompt, vigorous antibiotic therapy are emphasized. Surgical drainage, usually of the closed catheter type, frequently is necessary.

EDWARD W. HOPKINS

During the past decade, when resistant staphylococcal organisms were being recognized as serious problems in hospitals throughout the world, the highest rates of infection with these organisms were reported from the neonatal facilities of these institutions. Newborn nurseries, with their susceptible populations and high degree of contact between staff and patients, form an ideal environment for the harboring and propagation of staphylococci. Infections were manifested by pustules, omphalitis, conjunctivitis, mastitis, enteritis and sepsis, occasionally occurring in epidemic proportions.

Simultaneously, staphylococcal infections were becoming an increasingly difficult problem in pediatric and adult wards and in operating theaters. In all areas studied, observations bore out the vector problem and confirmed the spread of organisms by air, linen and equipment as well as from the skin and noses of both personnel and patients.

More recent reports have confirmed the earlier impression, as expressed by Barber and Whitehead[1] in 1949, that penicillin-resistant staphylococcal infections occurring in hospitals are nearly always cross infections. Certainly this statement is as true today as it was then.

Staphylococcal pneumonia in childhood, the subject of this presentation, would appear at first glance to represent the single exception

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TABLE 1

COMPARATIVE INCIDENCE OF STAPHYLOCOCCAL PNEUMONIA

YEAR	NUMBER OF CASES
1944	2
1945	4
1951	1
1952	4
1955	11
1956	19
1957	14
1958	23

to the rule. The incidence of primary staphylococcal pneumonia among infants and children outside the hospital population has increased significantly. With rare exceptions, these babies and children have become ill at home and have been hospitalized through outpatient facilities or on referral from practicing physicians. The explanation for this exceptional noninstitutional rate of staphylococcal infection would appear to lie in the fact that all the patients have in common a history of a relatively recent hospitalization—at birth—with an intimate exposure at that time to the staphylococci known to flourish in newborn nurseries. It is well recognized that persons can harbor these organisms for long periods of time and that in this susceptible age group the potential for production of disease might be expected to be high.

Study Material

During a four year period beginning in January 1955, 67 infants and children with staphylococcal pneumonia were hospitalized in the Harriet Lane Home, Baltimore. In 60 cases the pneumonia was considered to be primary, i.e., an underlying disease was not present. In the seven cases of secondary staphylococcal pneumonia the underlying disorders included agammaglobulinemia, cystic fibrosis of the pancreas, nephrosis, adrenal insufficiency, biliary atresia and chronic obstruction of the urinary tract.

A comparison of the incidence of staphylococcal pneumonia during random two year periods (1944 and 1945; 1951 and 1952) with the annual incidence in the present series reveals the striking increase (table 1). This rise in incidence occurred despite a general fall in the number of hospital admissions for pneumonia of all causes since the mid-1940s. That the increase is a general one is borne out by reports such as those of Briggs[2] in 1957 (27 cases in 34 months), Pryles[3] in 1958 (24 cases in 23 months), and Hendron and Haggerty[4] in 1958 (75 cases in six and one-half years, with a rising yearly incidence).

The majority of our patients were less than one year old, and 28 were three months old or younger (table 2). All 60 of the patients who had primary staphylococcal pneumonia had been born in hospitals, chiefly in large hospitals in the city. Careful review of the records for this group failed to reveal any significant abnormality of pregnancy, delivery, birth weight or general health of the infants prior to the onset of the pneumonia. Sixteen, however, had had known infections due to staphylococci while in the newborn nurseries or later.

TABLE 2

AGE OF PATIENTS AND MORTALITY RATE IN 67 CASES OF STAPHYLOCOCCAL PNEUMONIA

AGE	PRIMARY CASES	MORTALITY RATE (PER CENT)	TOTAL CASES	MORTALITY RATE (PER CENT)
3 months or less	25	17	28	24
4 to 12 months	20	5	21	10
1 to 6 years	14	0	16	7
More than 6 years	1	0	2	50
TOTAL	60	8.3	67	17.9

TABLE 3

CLINICAL FINDINGS ON ADMISSION IN 60 CASES OF PRIMARY STAPHYLOCOCCAL PNEUMONIA

SYMPTOM OR SIGN	NUMBER OF CASES
Tachypnea	52
Fever	46
Dyspnea	38
Cough	25
Distention of abdomen	14
Grunting	16
Cyanosis	9
Dullness over chest	44
Diminished breath sounds	48
Tubular breath sounds	8
Rales	29

TABLE 4

RADIOLOGIC FINDINGS IN 67 CASES OF STAPHYLOCOCCAL PNEUMONIA (60 PRIMARY CASES, SEVEN SECONDARY CASES)

FINDING	NUMBER OF CASES		
	Primary	*Secondary*	*Total*
Empyema	43	5	48
Pneumatoceles	53	3	56
Empyema and pneumatoceles	40	2	42
Empyema or pneumatoceles or both	59	5	64
Pyopneumothorax	14	1	15
Unilateral disease	53	5	58

Clinical Picture

The clinical picture at the time of admission to the hospital was variable, but generally the story was one of significant respiratory distress after an illness of three to four days' duration (table 3). Tachypnea and dyspnea were common, and more than one-fourth of the patients had respiratory distress severe enough to produce audible grunting with expiration. Mechanical respiratory difficulty appeared to be independent of febrile response or over-all toxicity of the infection. Abdominal distention was not uncommon and constituted a further handicap to respiratory effort.

Physical signs of disease in the chest also were quite prominent, in contrast to the usual findings in pneumonia in this age group. More than two-thirds of the patients had clear-cut localizing signs of consolidation, pleural reaction or limited air exchange, primarily unilateral.

Radiologic Findings

Radiologic findings were characteristic and representative of many of the classic changes hitherto described. Initial x-ray studies revealed changes ranging from homogeneous opacification to generalized emphysema associated with infiltration in a lobar configuration. Occasionally, air-containing cysts were seen in the initial x-rays; more often, these were observed on subsequent roentgenograms. Serial studies revealed marked variations as the disease progressed. A focal consolidation would develop subsequently into air-containing cysts which would change in size and shape in later films. A homogeneously opaque lung field would evolve dramatically into an air-fluid space, representing a large cyst with fluid level or a pyopneumothorax. The latter occurrence was common (23 per cent of the cases) and was observed in these patients both initially and later during the course of the disease (table 4).

Cysts of various sizes were typically thin-walled and infrequently contained fluid. The size of these cysts often changed strikingly, and sometimes they caused mediastinal shift or bulged across the midline of the chest.

Probably the most striking radiologic finding was the almost complete resolution of the changes, however severe, with healing. Minimal pleural thickening, increase of linear perihilar markings and occasional residual pneumatoceles, which eventually would resolve, were seen in follow-up films for at least several months but were considered very slight residuals radiologically.

Diagnosis

Radiographic changes were the primary diagnostic aid in this series. Empyema or pneumatoceles or both were seen in 95 per cent. Because of the relative rarity of empyema due to other pathogens, this finding would strongly suggest a staphylococcal infection and con-

TABLE 5

RESULTS OF CULTURES OBTAINED FROM CHEST, NASOPHARYNX AND THROAT

RESULTS OF CHEST CULTURES	SOURCE OF MATERIAL					
	Nasopharynx		*Throat*		*Nasopharynx, throat or both*	
	Cultures	Number positive	Cultures	Number positive	Cultures	Number positive
Positive (36 cases)	27	23	28	16	28	24
Cultures not made (31 cases)	26	21	25	18	26	24
TOTAL	53	44	53	34	54	48

stitute an indication for early and appropriate therapy. Despite the fact that in rare instances pneumatoceles occur in other forms of pneumonia, their presence is almost pathognomonic of staphylococcal infection. On two occasions during the four year period, air-containing cysts were seen in chest roentgenograms of patients who had pneumonia due to an organism other than staphylococci. One of these patients was proved to have pneumococcal pneumonia, and the disease in the other instance was due to a *Hemophilus influenzae* organism.

Bacteriologic confirmation of the diagnosis was obtained in all cases except two. In one of these two cases the clinical features and radiologic findings were classic. In the other, concurrent staphylococcal septicemia and a focus of extensive osteomyelitis of the humerus were considered adequate grounds for confirmation of the diagnosis.

The most consistently reliable source of material for culture of the organisms was the nasopharynx. Ninety per cent of cultures from this area yielded coagulase-positive staphylococci. The presence or absence of empyema did not alter significantly the results of cultures from the nasopharynx or throat. A positive culture was obtained from the nasopharynx, throat or chest in 97 per cent of the cases (table 5). Only seven of 46 blood cultures were positive (15 per cent), and in four of these seven cases a focus of infection such as osteomyelitis was present.

Sensitivity to the various antibiotic agents remained very constant in the cultures over the four years (table 6). The technic used was the standard disk method (Bondi and Spaulding). Early concern about the development of resistance to chloramphenicol, novobiocin and erythromycin appeared unfounded. Resistance to penicillin, streptomycin and the tetracyclines did not change. Material was not available for determining the emergence of resistance in a given patient during the course of the therapy.

Treatment

Two major types of treatment were employed in addition to general supportive measures, namely, antibiotic therapy and surgical drainage. A combination of chloramphenicol and erythromycin or chloramphenicol and novobiocin was given initially by the parenteral route and occasionally by the intravenous route to the sicker infants. In some of the cases seen early in the four year period, penicillin was given in large doses for long

TABLE 6

CULTURE SENSITIVITY OF VARIOUS ANTIBIOTICS DURING FOUR YEAR PERIOD

AGENT	TIMES TESTED	TIMES SENSITIVE	SENSITIVITY (PER CENT)
Chloramphenicol	55	50	92
ALBAMYCIN®	44	41	95
Erythromycin	54	46	85
Tetracycline	52	7	13
Chlortetracycline	11	1	9
Oxytetracycline	12	1	8
Penicillin	52	3	6
Streptomycin	44	2	5

periods, but later it was given only initially. The rationale for the use of penicillin was the hope that a sufficient amount of this bactericidal agent would be effective against even the resistant staphylococci. Dosages as high as 12 to 14 million units were given, initially by the intravenous route and then divided into intramuscular and oral components. Chloramphenicol was administered in a dosage of 100 to 150 mg. per kilogram of body weight per day; erythromycin, 30 to 50 mg.; and novobiocin, 30 to 40 mg.

Antibiotic treatment usually was continued for four to six weeks, but in some cases the course of therapy was longer. Therapy often was continued after the patients were sent home; after one or two weeks, a final assessment was made. The more prolonged treatment usually was dictated by tardy clearing of residual changes such as pleural thickening or persistent pneumatoceles.

The surgical management of staphylococcal pneumonia in infancy and childhood has been described thoroughly by Sabiston and associates.[5] Drainage, when indicated, was accomplished by insertion of an intercostal catheter attached to a closed system or water-seal suction. Needle aspiration, sometimes performed repeatedly, was adequate for removal of fluid or air, or both, in 20 cases, and insertion of a catheter was necessary for drainage in 28 cases. Closed drainage was used primarily to reduce the amount of empyemic fluid or relieve tension pneumothorax. On at least one occasion, the use of closed drainage appeared to accelerate resolution of a persistent pneumatocele which had recurred despite needle aspiration. On other occasions this technic was employed to relieve mechanical respiratory distress associated with pneumatoceles under tension. Neither antibiotics nor lytic enzymes were employed locally.

In one infant, a thick empyemic area and poor expansion of the lung necessitated open intercostal drainage and resection of a rib. The course of disease in this case was prolonged, and it became necessary after quiescence of the infection to perform a decortication of the lung, which was bound down by fibrotic pleurisy.

Mortality Rate and Follow-Up Observations

Five of the 60 patients who had primary staphylococcal pneumonia died (8.3 per cent). All seven patients whose staphylococcal pneumonia was secondary to underlying diseases died. Thus, the over-all mortality rate was 17.9 per cent (12 of 67 patients). Four of the five deaths in the primary group occurred within 72 hours after the patients were admitted to the hospital. All these infants were less than one year of age, and four were three months old or younger.

The period of hospitalization was usually five to six weeks. At the time of follow-up visits two to four weeks after dismissal from the hospital, the usual clinical picture was that of benign convalescence. Two patients had difficulty early in the follow-up period. One was the child in whom open drainage was necessary and who was sent home while the drainage tract was still open, to be readmitted later for closure of the tract. The other patient who had difficulty shortly after dismissal had a persistent pneumatocele which enlarged several weeks afterward to a size that produced mild respiratory difficulty; the lesion subsequently resolved spontaneously.

Follow-up examinations from one month to three years after hospitalization have yielded insignificant clinical and radiologic findings. Only minor residual radiographic changes have been observed in a few cases. A survey is presently under way to determine the normalcy of pulmonary function in these patients.

Discussion

As a clinical entity, staphylococcal pneumonia has not changed over the years. Macgregor[6] in 1936 published an excellent clinical and pathologic description of the condition; the mortality rate in his series was 100 per cent. Subsequent reports such as those by Kanof and co-workers,[7] Clemens and Weems,[8] Riley,[9] Blumenthal and Neuhoff,[10] and Forbes[11] documented a progressive decrease in the mortality rate associated with the use of surgical drainage and antibiotics. More recently, reports such as those of Bloomer and

associates,[12] Briggs,[2] Disney and co-workers,[13] and Pryles[3] have indicated that the incidence of staphylococcal pneumonia has been increasing. As long ago as 1946, Forbes[11] reported a striking rise in the relative incidence of staphylococcal empyema since the late 1930s, due chiefly to a reduction of complications of pneumonia caused by other organisms. The role of these other organisms in the recent rise in the absolute incidence of staphylococcal pneumonia and empyema is more indirect but subject to strong suspicion, by way of the alteration of institutional populations of microorganisms and subsequent contamination of susceptible hosts in wards or nurseries.

Information to be gleaned from the data reported herein does not differ greatly from that provided by other recent surveys. Certain points, however, might be emphasized. The unusual x-ray features of staphylococcal pneumonia favor an early specific diagnosis, and this expedites early specific therapy prior to laboratory confirmation. The fact that four of the five patients who died of primary staphylococcal pneumonia succumbed within 72 hours after admission to the hospital indicates the great need for prompt institution of treatment.

It would appear that considerable reliance in bacteriologic diagnosis can be placed on cultures from the nasopharynx. Certainly this is helpful as an aid to diagnostic confirmation, but a significant number of persons harbor nonpathogenic staphylococcal organisms. A survey of cases of pneumonia of all causes at the Harriet Lane Home over a period of several months disclosed that cultures of the nasopharynx were positive for hemolytic staphylococci in 35 per cent. Thus, a negative result of culture would have more statistical value than a positive one in a questionable case. Repeated cultures while the patient is in the hospital cannot be relied on, because the patient has been introduced to the organisms in the hospital environment and may well have become a carrier.

The preparation of smears from fluid obtained by needle aspiration or catheter drainage can provide real diagnostic help, and this practice should be routine.

Critical evaluation of treatment of staphylococcal pneumonia is very difficult. With the rapid progression of the disease leading to death in some cases and the benign course of survivors in others, one is hard pressed to evaluate the role played by specific components of the therapeutic regimen. For instance, the usefulness of penicillin has been particularly hard to assess. Early in the four year period covered by this survey, high dosages of penicillin were administered for long periods and occasionally unpleasant complications resulted. In two infants, sciatic palsies with permanent residual foot drop developed following multiple intramuscular injections of penicillin. Later, more concentrated solutions and multiple sites and routes of administration were used and this hazard was reduced. Initial use of penicillin may be motivated partly by uncertainty of diagnosis. This, coupled with the excellent prognosis after survival of the patient for two to three days, would encourage this observer to use penicillin initially in large doses and discontinue it after the first few days of treatment.

Surgical therapy is easier to assess, primarily because of the more immediate achievement of the therapeutic objective, which is the drainage of enclosed pus or the reduction of mechanical tension. Since the procedure of closed drainage has proved to be innocuous, one should resort to it when the need arises. However, each case must be evaluated individually as to factors such as the amount and tenacity of exudate, degree of tension or distress, and severity of infection.

One facet of the management of these patients is outstanding. A reduction in the mortality rate is likely to be achieved through early intensive treatment, particularly of the smaller and sicker infants. A prompt decision to initiate therapy, and prompt institution thereof, together with supportive measures and surgical treatment as indicated, may mean survival of some of these critically ill patients.

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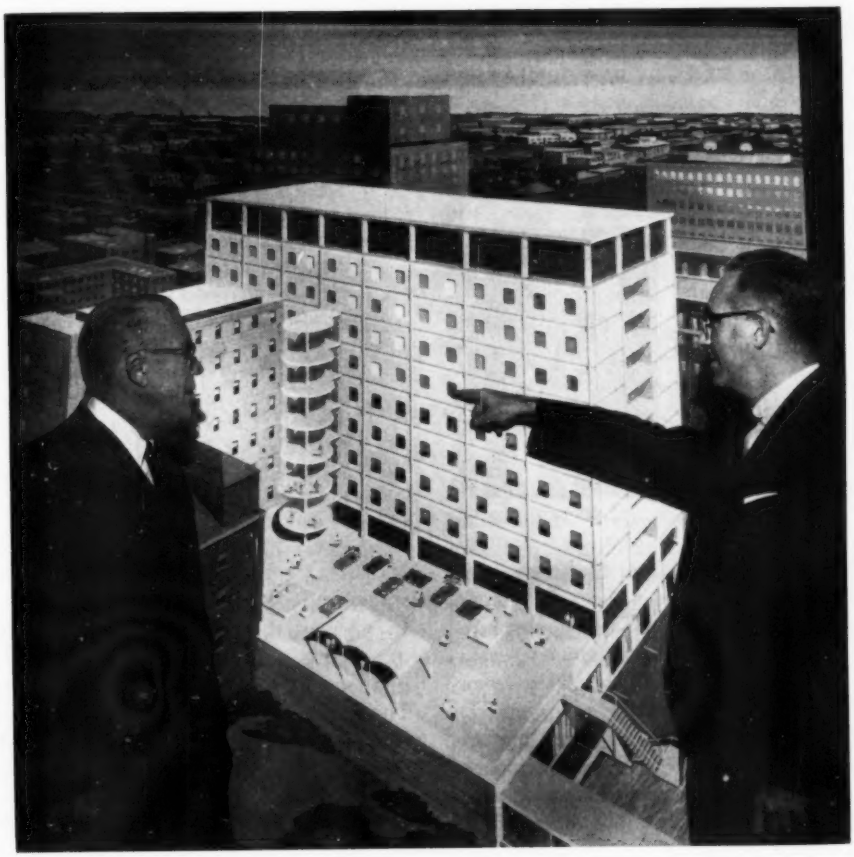

MODEL OF NEW HOPKINS CHILDREN'S MEDICAL CENTER

Dr. Milton S. Eisenhower (left), president of The Johns Hopkins University, and Dr. Russell A. Nelson, director of The Johns Hopkins Hospital, view sketch of the new Children's Medical Center to be completed in the spring of 1963.

Carcinoma in Situ of the Cervix

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What are the criteria for the microscopic diagnosis of carcinoma in situ *of the cervix? What evidence has been produced to indicate a relationship between carcinoma* in situ *and invasive cervical cancer? How should the preinvasive lesion be treated? These three questions are discussed, and clinical experience is presented based on 350 cases of carcinoma* in situ *in which hysterectomy was performed. None of the 350 women have died of cervical cancer.*

R. W. TELINDE

In the absence of a magic cure-all for cancer, the best that can be done is to detect the disease as early as possible and treat it by the means available, namely, surgery, irradiation or both. Over the past 15 years, in collaboration with Dr. Gerald Galvin and Dr. Howard Jones, I have directed much of my energy toward the early detection of cervical cancer. Gynecologists have an exceptional opportunity to detect the major pelvic malignancy, cervical cancer, because it is essentially a lesion of the exterior of the body. The cervix may be visualized and palpated, and smears and biopsies are easily obtained. Thus, we have a great advantage over those physicians who are attempting to detect early malignancy of the internal organs.

Today, as a result of cytology and our knowledge of carcinoma *in situ*, cervical cancer frequently is diagnosed in its preinvasive stage, when it is almost 100 per cent curable. In view of this high rate of curability, the question is quite properly asked, What is the relation of this disease to invasive cancer? This is an all-important question, because if there is no relationship the microscopic picture of carcinoma *in situ* has no practical significance. If a definite relationship can be established, the preinvasive lesion, because of its curability, may be the key to virtual elimination of the invasive disease and solution of the problem of cervical cancer.

There are three vital questions in connection with carcinoma *in situ* of the cervix: (1) How should the diagnosis be made, and what

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are the criteria for the microscopic diagnosis? (2) What evidence has been produced to indicate a relationship between carcinoma *in situ* and invasive cervical cancer? (3) How should the preinvasive lesion be treated? It is obvious that the answer to the third question depends on the answers to the first two questions.

Criteria for Microscopic Diagnosis of Carcinoma in Situ of the Cervix

Today, the diagnosis of carcinoma *in situ* usually is made as a result of suspicion aroused by positive or questionable findings of cervical cytologic study. This was not always the case. When Galvin and I first started working on this disease, we discovered it by performing cervical biopsy routinely for all women who were scheduled to undergo hysterectomy for benign disease. The cervical smear is a better method of ferreting out the condition, and although the final diagnosis should not be made on the basis of the smear alone, cytologic study is remarkably useful and accurate in directing suspicion toward the lesion.

One of the advantages of cytology is that it is much more accurate in detecting the *in situ* lesion than it is in detecting the advanced lesion. In the advanced invasive lesion there are always infection and necrotic cellular debris that tend to lessen the accuracy of diagnosis. The visible lesion of advanced invasive carcinoma may easily be subjected to biopsy, but carcinoma *in situ* is a disease without a sign or symptom and can easily be missed by biopsy. Cytologic examination, on the other hand, permits a view of the desquamated cells from all parts of the cervix, and if the examination is made by a competent cytologist the malignant cells are seldom missed.

In spite of the accuracy of cytologic examination, one should defer definitive therapy until the diagnosis has been confirmed by biopsy, conization, or both. There are very good practical reasons for this point of view. There is the slight possibility that the cytologist is in error. In addition, one must make every effort to determine the site and exact nature of the malignancy. A well-trained cytologist can be reasonably certain in differentiating malignant endometrial cells from cervical cells. He may even guess with considerable accuracy that the cervical lesion is invasive or noninvasive, but it is only a guess, not sufficient evidence on which to base definitive therapy. It is important to distinguish between invasive cervical cancer and preinvasive cervical cancer, for treatment of the two conditions is not the same.

The problem of establishing the diagnosis usually is presented to the clinician in the form of a report of a positive or suspicious smear. What should be the next step in establishing an exact diagnosis? Some physicians proceed directly to conize the cervix. We do not concur with this practice, because sometimes the question can be resolved by biopsy of the cervix as an office procedure.

The method of cervical biopsy is important. Remember that the surgical pathologist can only give you an opinion concerning the bit of tissue under his microscope. Therefore the random, hit-or-miss biopsy is not sufficient. Several bites of tissue should be taken with a sharp punch-biopsy instrument around the circumference of the cervix at the junction of the stratified squamous epithelium and the columnar epithelium. This junction usually is readily detected as a distinct line demarcating the light pink of the stratified epithelium from the red columnar epithelium. Many carcinomas *in situ* originate at this junction, but many others originate in the cervical canal, and therefore the biopsy specimen should include two or three bites of tissue from within the canal. The removal of tissue from the cervical canal may be difficult in a nulliparous woman, and in such a case if biopsy yields negative findings and the smear is positive one should proceed with a conization.

If the tissue obtained at biopsy shows stromal invasion, the lesion is classified as stage 1 and is treated as such without conization. If carcinoma *in situ* is found in the biopsy specimen, or if it is not found, cold-knife conization and curettage are carried out under general anesthesia. The conization should be done before the cervical canal is dilated and the cavity curetted, so as not to destroy the surface epithelium of the cervical canal. After

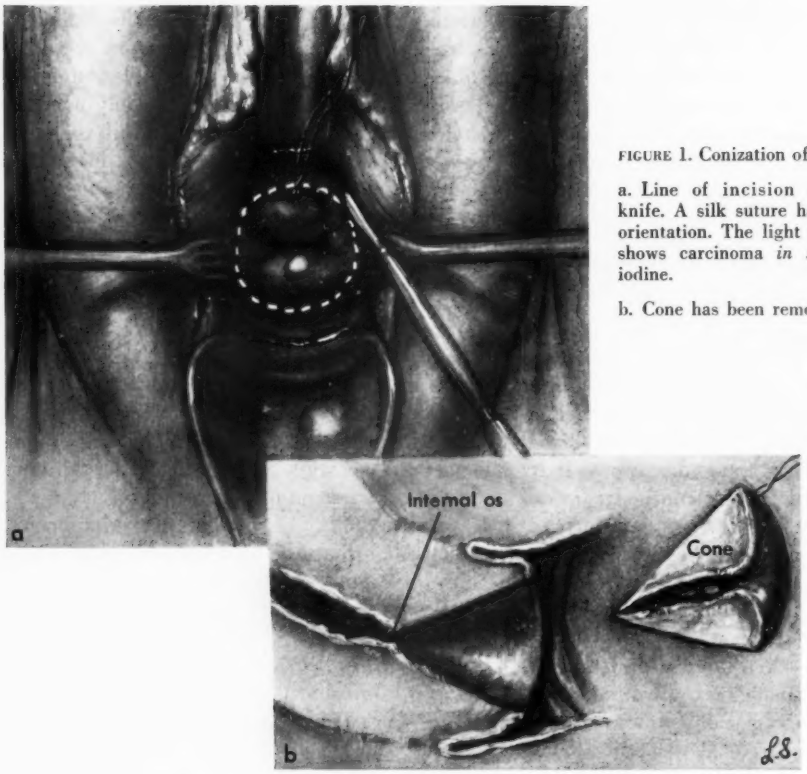

FIGURE 1. Conization of cervix.

a. Line of incision with small-bladed knife. A silk suture has been placed for orientation. The light area on the cervix shows carcinoma *in situ*, unstained by iodine.

b. Cone has been removed.

conization, the cervix is dilated and the uterine cavity is thoroughly curetted.

Many special instruments have been devised for conization, and they appear very clever theoretically, but a small-bladed knife is as good as any and better than most of them. The circumference of the cone should be close to the periphery of the portio, and the apex at the internal os (figure 1). Minimal bleeding can be controlled by placing a sponge against the area. If bleeding is troublesome, it usually can be controlled by placing a suture on either side of the cervix or, if this does not control the situation, by dissecting a flap of mucosa from the outer surface of the portio and suturing it over the oozing surface, as described by Sturmdorf. We prefer not to fulgurate the area, for two reasons. Fulguration spoils the specimen for ultimate study after hysterectomy, and the inevitable infection from the sloughing tissue accentuates the inflammatory reaction which complicates the operation of total hysterectomy if performed some days later. The cone is fixed and cut in the laboratory into five or six blocks. Many sections are cut from each block in order to determine the presence or absence of carcinoma *in situ* and its extent and to determine whether or not microscopic stromal invasion is present.

The next problem is one for the pathologist and concerns the minimal histologic criteria to justify a diagnosis of carcinoma *in situ*. In appearance, the individual malignant-appearing cells of carcinoma *in situ* do not differ from the cells of invasive cancer; the only difference is their position on the surface of the cervix. Similar cellular changes not infrequently are found in variable degree in the basal layers of cervical epithelium in a condition that we have chosen to call basal-cell hyperactivity. This condition will be discussed later, but suffice it to say at this point that we do

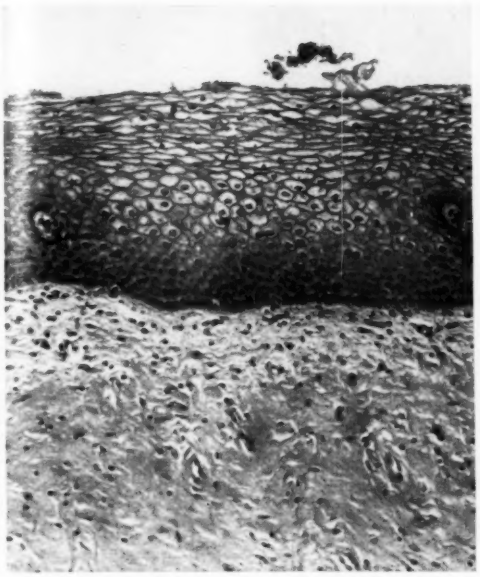

FIGURE 2. Normal cervical epithelium. Note the stratification from the basal cells to the transitional cells to the flat spinal cells on the surface. (x 150)

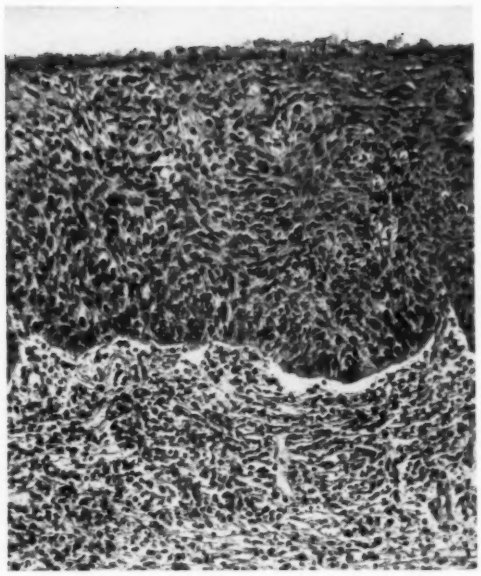

FIGURE 3. Carcinoma *in situ*. Note the complete lack of stratification of the cells and the hyperchromatic nuclei.

not consider it equivalent to carcinoma *in situ*. In our opinion, the minimal histologic changes for a diagnosis of carcinoma *in situ* should be the involvement of the *full* thickness of the epithelium by the malignant-appearing cells and a complete loss of the normal stratification of the epithelial cells.

Figure 2 shows normal cervical epithelium, with the basal layer, the transitional cells, and finally the spinal cells on the surface. In contrast, note the complete loss of stratification in figure 3, which illustrates carcinoma *in situ*. In our judgment, much of the difference of opinion which exists regarding the treatment of this condition stems from the difference in the criteria of the pathologists in making the diagnosis. The cervical glands frequently are involved by the abnormal epithelium which replaces the columnar epithelium and may eventually fill the entire gland. Even though the glands may be extensively involved, the case is still classified by common agreement as carcinoma *in situ* (figure 4).

When there is microscopic invasion of the stroma, the lesion is classified as stage 1 and in our clinic is treated primarily by irradiation. Difficulty arises when there is disagreement among pathologists concerning minimal stromal invasion. Although this poses a problem about which pathologists can argue indefinitely, the clinical decision is not too difficult. When invasion is so slight that it is debatable, we have treated the cases as carcinoma *in situ*, and our results have not caused us to regret this decision.

Of considerable pathologic and clinical importance is the differential diagnosis of carcinoma *in situ* and basal-cell hyperactivity. In the latter condition some of the cells in the deeper layers of the epithelium show some degree of mitosis and hyperchromatism (figure 5). This microscopic picture is frequently seen around the periphery of carcinoma *in situ*, just as the latter condition often is seen to involve the epithelium surrounding invasive cancer. Galvin has made a special study of basal-cell hyperactivity and has found that the greater the degree of involvement of the epithelium by these abnormal cells the greater is the likelihood that a diagnosis of true car-

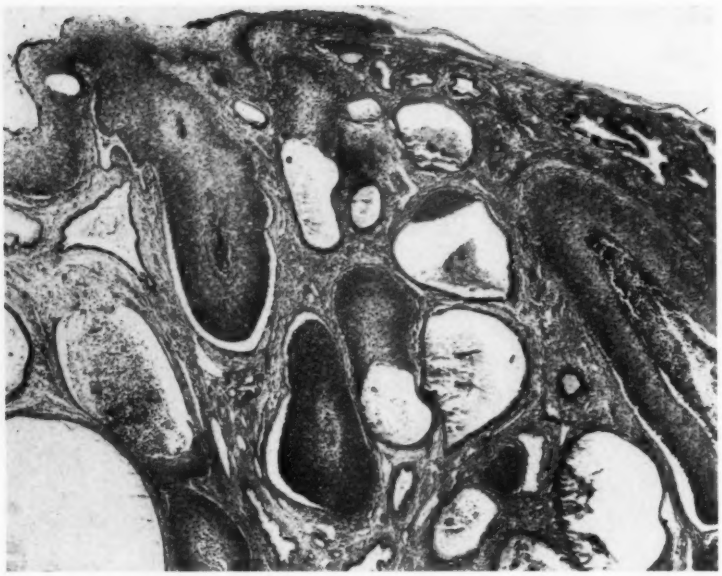

FIGURE 4. Carcinoma *in situ* showing extensive glandular involvement. (x 30)

cinoma *in situ* will eventually be made. From his studies we have concluded that the practicing gynecologist should regard a diagnosis of basal-cell hyperactivity as a warning that carcinoma *in situ* may exist or that it will ultimately develop. Smears and biopsies should be taken in such cases until a diagnosis of carcinoma *in situ* is made or until all suspicion has disappeared. It is well to remember that preinvasive cervical cancer does not constitute an emergency. Usually years elapse before invasive cancer develops, and therefore when there is doubt there is ample time for follow-up of the patient with repeated smears and biopsies until a diagnosis can be definitely established.

Relation of Carcinoma in Situ to Invasive Cancer

Although the histologic picture of carcinoma *in situ* is interesting, it has no clinical significance unless its relation to invasive cancer can be established. Hence we must answer the question, What evidence has been produced that would indicate this relationship? Histologic and clinical evidence has been produced on this point. In many instances, advanced invasive cancer is surrounded by a zone of carcinoma *in situ*, the cells of the invasive lesion being indistinguishable from those of the preinvasive lesion. We have observed all degrees of carcinoma *in situ* and invasive cancer in the same cervix, i.e., surface involvement alone, surface involvement with glandular involvement, and these two conditions in close proximity to real stromal invasive cancer. We have even seen the surface lesion extend to the very top of the endometrial cavity, becoming highly invasive there. Galvin, Jones and I have also made a retrospective clinical study of 723 cases of invasive cancer treated in our clinic over a period of years. In 13 cases, a previous biopsy was performed in our clinic from one to 17 years before. The slides were still in our laboratory, as well as the blocks of tissue. We restudied this material and made more sections from several of the blocks. In one of the 13 cases, no epithelium could be found in the sections. Eleven of the other 12 specimens showed carcinoma *in situ*. This incidence is too high to be a matter of coincidence, and therefore we believe that carcinoma *in situ* precedes invasive cervical cancer in a high percentage of cases. It is impossible to know the exact percentage. Perhaps it is 100 per cent, but in

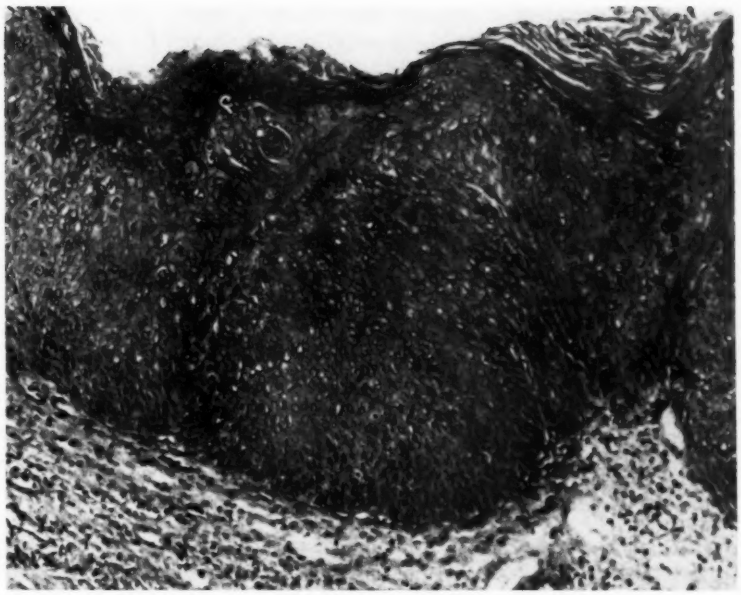

FIGURE 5. Basal-cell hyperactivity. The darker-staining cell mass in the center contains many mitoses but these abnormal cells do not constitute the full thickness of the epithelium. (x 150)

our series it was 11 out of 12. This does not mean that all carcinomas *in situ* develop into invasive cancers. Since it is known that many years may elapse between the discovery of carcinoma *in situ* and the appearance of clinical cancer, it is probable that many women die of other causes before invasive cancer ever develops.

We have not deliberately followed a group of women who have carcinoma *in situ* and have not received treatment to determine their future fate, but Peterson of Copenhagen has. He found that of 123 patients so observed, invasive cancer developed in one-third within nine years. We have had an accidental experience, however, which has thrown some light on this phase of the subject. In six cases in which the diagnosis of carcinoma *in situ* was made, in various hospitals in Baltimore, and in which the patients were lost to follow-up either because the patient failed to cooperate or because the attending physician did not follow the patient carefully or give her complete treatment, the women eventually were seen in our clinic with invasive cervical cancer. This pathologic and clinical experience strongly supports our view that there is a definite relationship between preinvasive and invasive cervical cancer.

Treatment of Preinvasive Carcinoma

Because we believe that carcinoma *in situ* and invasive cervical cancer are related, we have tended to recommend hysterectomy for women with carcinoma *in situ*. When our study of this disease was just beginning, as already stated, the carcinomas *in situ* were discovered by biopsy of the cervix in women who were to have a simple total hysterectomy for benign disease. This operation was employed for our first cases, but for the past several years we have modified the procedure to include removal of a moderate amount of parametrium and a cuff of the vagina.

We have now operated on 350 women for carcinoma *in situ* of the cervix. There have been eight recurrences, all in the upper vagina. In recent years we have insisted on a Schiller test before a hysterectomy, to determine the extent of the disease. This test is not infallible, but often it is helpful in determining the extent of the vaginal cuff to be removed. We have, in fact, found some vaginal lesions at quite a distance from the involved cervix,

without any apparent continuity. Such cases cause one to wonder about the possibility of multicentric origin of the lesion.

Ureteral catheterization is a routine operative practice, to enable us to remove parametrial tissue without dissecting out the ureters. Ureteral fistulas have not developed.

Malignant involvement lateral to the cervix was found in only two of the 350 cases. In one, the parametrial tissue was invaded, and in the other an enlarged metastatic gland was discovered. Obviously these cases were misjudged preoperatively. In the case in which the involved gland was discovered, the surgeon performed a typical Wertheim operation with pelvic lymphadenectomy, and in the case of parametrial involvement the operation was stopped and the patient was treated with irradiation.

Since many women with carcinoma *in situ* are relatively young, the question of ovarian removal arises. The average age of our patients was 37 years, but several were in the third decade of life. The ovary is a late and infrequent site of metastasis of even advanced cervical cancer, and therefore it seemed to us to be logical and safe to save one or both ovaries in women less than 40 years of age. The patients whose ovaries were conserved have all remained well. The fact that ovarian function can be preserved in the young women has been a major factor in our decision to treat these patients surgically rather than by means of irradiation. In eight cases, surgical treatment seemed contraindicated because of the medical condition of the women. One of these eight women died of cancer within six months of her treatment. Postmortem examination disclosed metastatic cancer, and it seems probable that invasive cancer existed at the time of treatment, although we were unable to prove this.

The question of childbearing also enters into the decision of treatment of these relatively young women. It has been our policy to tell the patient frankly that she has a lesion which is not cancer in the usual sense but may develop into invasive cancer in the course of her lifetime. Thus far, all the patients have elected to have hysterectomy and, if they have not had children, to adopt them or remain childless. Other workers in this field have permitted some of the younger patients to have children. It is a calculated risk which should be left to the patient's judgment after she has been given a full understanding of the condition. We have discovered carcinoma *in situ* in several pregnant women, and have performed hysterectomy during pregnancy in only three cases. In each instance the woman had an ample family and the lesion was particularly malignant-looking histologically. The activity of the cervical epithelium during pregnancy can make the diagnosis of carcinoma *in situ* more difficult, but in each case in which we made an unequivocal diagnosis during pregnancy the diagnosis was substantiated when a repeated study was made after termination of the pregnancy.

This, then, represents the experience of one clinic with carcinoma *in situ* of the cervix. Of 350 women who were treated by hysterectomy, none have died of cervical cancer. The eight women who had recurrences in the vaginal vault have been treated by complete vaginectomy or by irradiation and they are clinically well.

We believe that vaginal cytology and the application of our present knowledge of the life history of carcinoma *in situ* can eventually eliminate invasive cervical cancer. All that is required are the education of women and physicians and the translation of this knowledge into action. Annual pelvic checkups on all American women, including cytologic smears, should, in the course of a decade, make invasive cervical cancer as rare as typhoid fever is today.

Collaborative Glaucoma Survey

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A number of institutions, including The Johns Hopkins University, are participating in a collaborative study of chronic simple glaucoma. It has been estimated that there are 800,000 persons in the United States who are unaware that they have glaucoma. The disease produces blindness in about 3400 persons each year. Preliminary findings of the survey are presented. When tonometry, tonography and the water-drinking test have been well evaluated in the early diagnosis of chronic simple glaucoma, an efficient screening program can be designed and much visual disability prevented.

CARTERET LAWRENCE

GLAUCOMA is a disease of the eye that is generally associated with increased intraocular pressure and eventual change in the field of vision. There are many types of glaucoma,[1] the most insidious and most common being chronic simple glaucoma. Between 2 and 10 per cent of persons more than 40 years of age have some evidence of this disease. There is an obstruction in the outflow passages for aqueous, possibly in the trabeculae, the loose meshwork of tissue through which the aqueous filters on its way to the canal of Schlemm and the venous capillaries. Initially the disease does not produce symptoms, but eventually it causes optic atrophy and characteristic change in the visual field.

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It has been postulated that the elevated intraocular pressure (24 mm. Hg or higher) slowly damages the eye by embarrassing the capillary circulation of vessels supplying the optic nerve where it reaches the globe, causing atrophy of the axons in the optic nerve and eventual loss of the ganglion cells in the inner retinal layer. The rest of the retina ordinarily

remains normal, but there is a characteristic restriction of the visual field and a loss of tissue in the optic disk, called glaucomatous cupping.

This theory for the effect of elevated intraocular pressure fits the known clinical findings quite well. Prolonged elevation of intraocular pressure produces the changes described. The higher the intraocular pressure, the quicker the functional and anatomic changes develop. Systemic hypertension without major vascular disease appears to protect the eye against the effects of elevated intraocular pressure.[2] Conversely, in older persons the functional and anatomic changes of glaucoma occasionally develop without any evidence of elevated intraocular pressure; the explanation for this may be a reduction in capillary pressure due to arteriosclerotic vascular change.

Most ophthalmologists feel that usually they can prevent the earlier changes in the optic nerve when they maintain intraocular pressure at a normal level. Once damage to the optic nerve is well started, it sometimes will continue despite normalization of intraocular pressure.

With the foregoing in mind, it becomes hard to define chronic simple glaucoma exactly.

Collaborative Study of Chronic Simple Glaucoma

In an effort to define chronic simple glaucoma more exactly, a collaborative study is being undertaken by a number of institutions, namely, The Johns Hopkins University in Baltimore, Washington University in St. Louis, University of California in San Francisco, and the State University of Iowa in Iowa City. The close blood relatives of patients with all the signs of chronic simple glaucoma will be followed carefully for five or more years. The intraocular pressure, aqueous outflow system, and function and anatomy of the optic nerve will be studied to evaluate the prognostic significance of various clinical tests.

The intraocular pressure is measured in two ways, with the Schiötz tonometer and with the Goldmann applanation tonometer. The Schiötz tonometer is an indentation tonometer which displaces some 17 mm.[3] of aqueous and raises normal intraocular pressure some 15 mm. Already elevated intraocular pressure is raised even higher. Extrapolation of the elevated, measured value to the previous undisturbed value is made with a table of average values and is not very accurate. With the Goldmann applanation tonometer the cornea is flattened rather than dimpled. The force required to produce an area of flattened cornea exactly 3.06 mm. in diameter provides an accurate estimate of the intraocular pressure in an eye with a normal cornea. The intraocular pressure during measurement is about 0.5 mm. higher than it was before measurement.

Intraocular pressure has a normal diurnal variation of less than 6 mm. Characteristically the diurnal variation is higher in early simple glaucoma. It has been estimated that in a survey based on only one measurement of intraocular pressure some 20 per cent of the cases of simple glaucoma would be missed, whereas if repeated measurements of pressure were made on successive days, at different times of day, very few would be missed, even by pressure measurement alone.[3]

An aid to earlier diagnosis of glaucoma is tonography. The Schiötz indentation tonometer is left on the eye for four minutes. If the inflow of aqueous is assumed to be constant during this period, we can estimate the extra volume of aqueous pushed out of the eye by the measured increase in intraocular pressure. We arrive at a measure of the ease with which aqueous is forced from the eye by intraocular pressure. This measure is called facility of outflow. As glaucoma simplex becomes established, facility of outflow falls, so that for a given inflow a higher intraocular pressure is required to maintain outflow and inflow at equal volumes.

Drinking a liter of water on an empty stomach changes the osmotic values of the plasma sufficiently to increase intraocular pressure and decrease facility of outflow in chronic simple glaucoma. Thus, tonography performed before and after ingestion of a liter of water may provide the most reliable guide to the earliest diagnosis of glaucoma simplex.[4] It also may give some idea of the prognosis.[5]

We must not forget that our prime interest

is in preservation of function, namely, vision. The part of vision that is most severely affected by glaucoma is the visual field, and the anatomic change best correlated with loss of visual field is the degree of cupping of the optic nerve. In the collaborative survey, this cupping is described in detail for each patient, and at some institutions it will also be photographed.

We have chosen our study population so that we will have the best opportunity to follow the subjects (initially nonglaucomatous by our best clinical tests) during the time when all the important changes of glaucoma are developing.

Tonography rests on rather uncertain experimental grounds. Many investigators feel that inflow is not constant during the procedure. Quite possibly, facility changes with changing pressure.[6] The volumetric calibrations of the Schiötz tonometer itself are only approximate. Many tonographic studies have been comparisons of findings in patients who have obvious glaucoma simplex with findings in subjects with obviously normal eyes. Thus, separation of the two groups has been somewhat artificial and not representative of the whole population. We hope that by studying the parents, siblings and children of persons who have characteristic loss of visual field due to glaucoma we will have a complete spectrum of subjects from the normal to the definite advanced simple glaucoma. This will afford a better empiric evaluation of tonography.

The diagnosis of glaucoma simplex will be made only when the typical arcuate scotoma is present and other reasons for such a scotoma are absent. Intraocular pressure and the tonographic response to the water-drinking test will not be used as end points, because one of the purposes of the study is to determine the prognostic importance of different elevations of intraocular pressure, positive reactions to the water-drinking test, and so on.

Subjects whose intraocular pressure is less than 30 mm. Hg will not be treated until Bjerrum's scotoma or loss of visual field is evident. Since any intraocular pressure of more than 21 mm. Hg is suspicious, subjects whose intraocular pressures are between 21 and 30 mm. Hg will have frequent visual-field examinations.

When we have enough records of persons who initially have normal visual fields and in whom the changes of chronic simple glaucoma develop, we will be able to compare the intraocular pressures and outflow facilities before and after ingestion of water with these values in another group of subjects of the same age in whom the visual-field changes have not developed.

Age is an important consideration. Many workers feel that facility of outflow decreases with increasing age and that aqueous inflow decreases, so that the normal population does not have increasing intraocular pressure with advancing age.[7]

It was decided to study the families of patients who have typical chronic simple glaucoma to increase the number of persons in the study population in whom glaucoma develops. This choice of study group has the theoretical disadvantage that the glaucoma simplex which occurs among persons related to glaucoma patients might be different from that which occurs independent of such a family history. I do not feel that there is any evidence that chronic simple glaucoma in families is different from glaucoma in persons with presumably negative family histories. Our preliminary results seem to indicate that the levels of intraocular pressure, facility of outflow, and response to water tend to be similar in families just as body weight, height, complexion, etc. tend to be similar.

Our preliminary results also indicate that some tonographic criteria which have been proposed for diagnosing early glaucoma lead to too high an incidence of abnormality. For example, Becker[4] examined the ratio Po/C where Po is the initial undisturbed intraocular pressure in millimeters of mercury and C is the facility in millimeters^3/millimeters of mercury per minute. He found that Po/C was less than 100 in his group of normal control subjects and greater than 100 in his group with glaucoma. Since the separation of his glaucoma population from his normal control population was excellent, he proposed that this ratio be used as a diagnostic index. Using

the same tests on the employees of a department store who were more than 35 years of age, we found that 25 per cent had a ratio of Po/C greater than 100, whereas the incidence of chronic simple glaucoma is from 2 to 10 per cent.

Following these patients from year to year, we are finding that the tonographic findings are very repetitive, and thus they may well characterize a person's aqueous dynamics. It is our hope that by determining the character of aqueous dynamics we will eventually be able to predict a patient's chances of losing visual field without treatment, with medical treatment, and with surgical treatment.

Ideally we should know something about the intravascular pressures around the optic nerve. Unfortunately, ophthalmodynamometric determination of systolic and diastolic pressure in the central retinal artery in a few patients who have soft glaucoma has not revealed anything significant. "Soft glaucoma" is a rare condition in which the characteristic visual-field and optic-nerve changes of chronic simple glaucoma are seen, but there is no elevation of intraocular pressure (as determined with the applanation tonometer) at any time during the diurnal pressure cycle. It is possible that we may have an approach to this problem by using Dr. Goldmann's technic, which shows that the changes analogous to Bjerrum's scotoma can be elicited in normal eyes when the intraocular pressure is raised artificially with a dynamometer.[8] For this type of study, light-sense perimetry is superior to ordinary perimetry. However, this type of examination is very difficult to conduct and would be impractical in a study program which already is long enough to tire and discourage the subject.

When tonometry, tonography and the water-drinking test have been well evaluated in the early diagnosis of chronic simple glaucoma, then an efficient screening program can be designed and much visual disability will be prevented.

It has been estimated that there are 800,000 persons in the United States who are unaware that they have glaucoma. Approximately 3400 persons become blind from glaucoma each year. Most of these cases of blindness would have been preventable if treatment had been started early.

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Exocrine Secretions in Cystic Fibrosis of the Pancreas

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The findings of various investigative studies of the composition of glandular secretions in cystic fibrosis of the pancreas are presented. The duodenal fluid, secretion of the bronchial glands, saliva, tears and sweat are abnormal in this metabolic disease. Abnormalities of composition, viscosity, and electrolytic and organic components and their relationship to rate of secretory flow are reviewed, and other conditions are mentioned in which some of these abnormalities may be found.

THE composition and the mechanism of formation of glandular secretions have attracted increasing interest in recent years (table 1). The control of glaucoma, incipient hydrocephaly and gastric ulcer by drug therapy has resulted from a study of the physiology of the ciliary body, choroid plexus and parietal cells of the stomach. However, the disorder in which the most widespread alteration in glandular function has been observed is cystic fibrosis of the pancreas.

As is now well known, cystic fibrosis of the pancreas is a generalized metabolic disease wherein the pancreatic involvement may at times be relatively mild and a less important determinant of mortality and morbidity, although the pathogenesis of the pancreatic defect is of great interest. The chief clinical problem with this group of patients is the management of the chronic pulmonary disease and concomitant infection, both of which seem to occur as a consequence of the abnormal secretion of the bronchial glands. Also of clinical interest, but to a lesser extent, is the abnormality in hepatic secretion which occasionally leads to the occurrence of biliary cirrhosis.

Perhaps the most striking secretory abnormality in cystic fibrosis of the pancreas is the elevation of the concentration of electrolytes in the sweat. It is this discovery, by Darling and associates,[1] that has been interpreted as an indication that cystic fibrosis of the pancreas is more than a defect in mucus-secreting glands.

Duodenal Fluid

The first striking abnormality of secretion to be noted in cystic fibrosis was that of duo-

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denal fluid,* which is composed of pancreatic fluid with the addition of bile and fluid from the duodenal glands. Normally, duodenal fluid is a golden-colored, slightly viscous fluid containing the enzymes amylase, lipase, protease, carboxypeptidase and chymotrypsin (see table 2). Its electrolytic concentration, while always isotonic, normally varies considerably with the rate of flow.[3] At low rates of secretion the fluid is composed mainly of sodium and chloride, and the concentrations of bicarbonate and potassium are low. As the secretory rate increases, the fluid remains isotonic but the concentration of chloride falls while that of bicarbonate rises.

In cystic fibrosis the electrolytic concentration of duodenal fluid is reported to be within normal limits,[4] but there is little evidence to prove that this is the case at all rates of flow.

The striking abnormality in duodenal fluid of patients with cystic fibrosis concerns its enzymatic content and viscosity. Depending on the degree of pancreatic involvement, there is usually a pronounced increase in the viscosity (as measured by the Ostwald viscosimeter) and an equally marked decrease in enzymatic activity. Table 2 summarizes Schwachman's[5] findings in his studies of duodenal fluid.

Dische and co-workers,[6,7] in an attempt to gain insight into the fundamental defect resulting in the abnormal viscosity of duodenal fluid in cystic fibrosis, undertook intensive studies of its mucoprotein fractions. It was found that duodenal fluid of patients with cystic fibrosis contains a mucoprotein which, after treatment with organic solvents, loses its solubility in water. Moreover, certain fractions of the mucoproteins have altered carbohydrate-to-protein ratios as well as an abnormal content of sialic acid. These changes can reasonably be considered responsible for the abnormalities of solubility and viscosity in duodenal fluid of patients with cystic fibrosis.

Secretion of Bronchial Glands

The most challenging and perplexing problem in cystic fibrosis from both the clinical and the investigative points of view is the secretion of the bronchial glands. The extreme viscosity of this secretion is immediately apparent to anyone who sees it. Comparative quantitative measurement of viscosity of an unhomogeneous fluid is somewhat uncertain, but attempts have been made to quantitate the viscosity of tracheobronchial secretions[8] and they have been found to be about five times more viscous than the secretions of control subjects.

In addition to measurement of viscosity, attempts have been made to study the electrolytic and organic components of material obtained from the tracheobronchial tree in cystic fibrosis and in bronchiectasis.[9,10] These studies indicate that the sputum of patients with cystic fibrosis has a lower electrolytic content when calculated on a dry-weight basis. Also of interest is a higher content of nucleic acid in cystic fibrosis. It is difficult to know how much significance to attach to these differences. Bronchiectatic fluid would appear to be composed of secretions and products of inflammation from a relatively distal part of the tracheobronchial tree, whereas the secretions one obtains from patients with cystic fibrosis may contain considerably more fluid from the trachea and upper bronchi.

*Duodenal fluid is best obtained[2] by passing a No. 10 or 12 rubber or plastic catheter (moistened with mineral oil) through the nose, into the stomach, along the greater curvature and then into the duodenum. It may be necessary to use fluoroscopic control briefly to aid in pointing the tip of the tube. When the tube is in the duodenum, the fluid will flow spontaneously (although occasional gentle suction is necessary). Testing with NITRAZINE® paper should yield a high pH unless there is significant contamination from gastric acid. It may be necessary to pass a small amount of olive oil down the tube to accelerate the production of duodenal fluid. The fluid should be collected in test tubes placed in an ice bath.

TABLE 1

APPROXIMATE NORMAL COMPOSITION OF VARIOUS SPECIALIZED EXTRACELLULAR FLUIDS (EXPRESSED IN MILLIEQUIVALENTS PER LITER)

FLUID	CHLORIDE		SODIUM		BICARBONATE		POTASSIUM*
	Low rate of flow	*High rate of flow*	*Low rate of flow*	*High rate of flow*	*Low rate of flow*	*High rate of flow*	
Sweat	10	45	10	60			10
Parotid and submaxillary fluid	10	40	10	80	20	60	10.0
Sublingual saliva	165*		165*				
Tears	128*		146				15
Pancreatic fluid	120	20	150	150	20	120	7
Aqueous humor	126*		150*		22*		5
Parietal gastric juice		162		5			11
Bile	40	60	145	145	10	60	7

*Concentration not directly dependent on rate of flow.

Parotid and Submaxillary Glandular Secretion

Other secretions are of less importance from a standpoint of symptomatology than duodenal and bronchial secretions, but saliva, tears and sweat are abnormal and deserve consideration for an understanding of the complex nature of cystic fibrosis of the pancreas.

The parotid and submaxillary glands normally secrete a watery fluid* in which the concentration of electrolytes varies greatly with the rate of flow.[12] At low rates of flow the fluid is hypotonic with very low concentrations of sodium, chloride and bicarbonate. As the rate of flow increases, the concentration of these substances increases. The tonicity approaches, but does not equal, that of extracellular fluid, although the concentration of bicarbonate may be more than twice that of serum. The concentration of potassium is independent of rate of flow and usually is two to three times the level in the serum.

Saliva

Sublingual saliva is somewhat different in that it appears to be isotonic at all secretory rates and is a solution mainly of sodium chloride. It is of interest that the concentration of chloride in sublingual saliva is considerably higher than the value for chloride in the serum.

In addition to the usual electrolytes, salivary glands have the ability to elaborate fluid with concentrations of thiocyanate and iodide greatly in excess of the serum values at low secretory rates. As the rate increases, the concentration of both iodide and thiocyanate decreases.[13]

Although few studies of patients with cystic fibrosis have been made in which careful attention has been paid to the effects of the rate of salivary flow on the composition of saliva, it appears[14-17] that both mixed saliva and parotid saliva have increased concentrations of sodium and chloride when compared with control values. However, concentrations of iodide and thiocyanate are normal in patients with this disease.[18] Unfortunately, these salivary abnormalities, real as they are, cannot be used diagnostically because there is considerable overlap between control subjects and patients with cystic fibrosis. The previously cited studies also disclosed that the patients with cystic fibrosis apparently responded to given secretory stimuli with a higher rate of flow than did control subjects.

Cystic fibrosis is not the only clinical situation in which elevated salivary electrolytes have been noted. A newborn infant during the first few weeks of life may demonstrate ele-

*Parotid or submaxillary saliva can be obtained by dilating the ductal orifices with Bowman probes and passing small polyethylene catheters. Alternatively one may use a double-lumen suction device[11] which can be placed over the orifice to Stensen's duct. Reflex stimulation of flow can be obtained with lemon juice or other suitable stimulant.

TABLE 2

VISCOSITY AND ENZYMATIC ACTIVITY OF DUODENAL FLUID*

TEST	HEALTHY INFANTS AND CHILDREN	COMPLETE PANCREATIC INSUFFICIENCY	PARTIAL PANCREATIC INSUFFICIENCY
Viscosity time (minutes)	Less than 3	More than 3 in 87% of patients	More than 3 in approximately 70% of patients
Amylase (units)	4.20	0-1	0.20
Less than six months	0	0	0
Lipase (units)	3-10	0-1	0-10
Protease (units)	18-70	0-2.5	0-70
Carboxypeptidase (milligrams betanaphthol)	0.40-1.00	0-0.40	0.00-1.00
Chymotrypsin (milligrams betanaphthol)	11-65	0-5	0-65

*From data of Schwachman.[5]

vated electrolytic concentrations,[19] and adrenal insufficiency may inconstantly lead to an increase in concentration of sodium in the saliva.[20]

Tears

The secretion of the lacrimal glands,* which normally is isotonic (being composed chiefly of sodium chloride[21]), also has been noted to be abnormal in cystic fibrosis.[16] While the differences are not great, the concentrations of sodium and chloride are elevated slightly. Alteration in the lysozyme content of tears has not been noted.

Sweat

The sweat glands† normally elaborate fluid in which the electrolytic components bear some resemblance to parotid saliva. At low rates of flow the fluid is quite hypotonic, and the electrolytic concentrations increase as the rate of flow increases.[23] Sodium and chloride constitute its chief ions. The value for potassium, while greater than that of serum, does not change with alterations of rate of flow.

In cystic fibrosis, the concentrations of sodium and chloride in sweat are almost invariably two to five times the normal values. Whereas the chloride content of normal sweat may vary from about 10 to 40 mEq. per liter, in cystic fibrosis it may be from 60 to 120 mEq. per liter. This difference is so clearly defined that the diagnosis of cystic fibrosis of the pancreas would be doubtful if the concentration of chloride in the sweat were normal, although there have been rare cases in which clinical signs and symptoms were indistinguishable from cystic fibrosis and typical findings of this disease were noted at necropsy but the electrolytic composition of the sweat was normal.

There are, however, three other clinical situations in which the value for chloride in the sweat can be relatively high. Adrenal insufficiency is well known to produce high electrolytic concentrations in sweat.[24] In addition, a small percentage of parents and siblings of patients with cystic fibrosis have somewhat elevated concentrations of chloride in the sweat. Warming-Larsen and Wallace[25] reported that during the edematous stage of nephrosis the electrolytic composition of sweat was elevated while the rate of sweating was depressed. Concentrations of sodium of about 100 mEq. per liter were noted. These values

*Tears are obtained by placing a weighed pledget of cotton within the conjunctival sac. After a period of time the pledget is reweighed and the fluid leached by an appropriate diluent.

†There are many methods to collect sweat, but perhaps the easiest and safest is that described by Gibson and Cooke.[22] It employs pilocarpine iontophoresis followed by absorption onto weighed paper from which the fluid is leached after collection.

everted to normal with the onset of diuresis, although the edema had not disappeared. Brodkey and Gibbs[26] recently demonstrated that in addition to elevated concentrations of sodium chloride in sweat of patients with cystic fibrosis there also appears to be an elevated sweat-to-serum ratio of iodide.

Preliminary observations by Sabinga[27] indicate that patients with cystic fibrosis exhibit a few other rather interesting sweating phenomena. They have elevated rates of sweating at night, although with repeated stimulation their sweat glands appear to fatigue earlier. Of particular importance is Sabinga's observation that at very low rates of sweating the electrolytic concentrations may be normal.

Other substances in sweat have been studied, but as yet no other discrete abnormality has been observed. Notably, urea concentration[28] and amino-acid patterns[29,30] have been normal.

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Intracardiac Surgery Performed With Cardiopulmonary Bypass

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The conduct of cardiopulmonary bypass and the apparatus in use at The Johns Hopkins Hospital are described, including some recent improvements in technic. Some 450 operations in which the pump-oxygenator has been used are summarized briefly, with reference to the types of lesion treated, the indications for operation, fundamentals of treatment, and survival rates.

CARDIOPULMONARY bypass has been employed in an increasingly large proportion of intracardiac surgical procedures at The Johns Hopkins Hospital in recent years. At present it is used in about half of the surgical procedures for treatment of congenital cardiac defects and in a smaller percentage of operations for acquired cardiac conditions. At the end of September 1960, 450 operations had been performed in which the pump-oxygenator was used. We shall recount the experience on which our present methods are based and describe some recent improvements in technic. Open intracardiac surgical procedures in which hypothermia and caval occlusion were employed have been reported elsewhere.[1] We continue to use hypothermia and caval occlusion for most patients with atrial septal defect (except adults) and for some patients with isolated pulmonary stenosis.

Apparatus

The pump-oxygenator in use at present represents a departure from the Gaertner-Kay modifications of the Gibbon screen-oxygenator, with which most of our early work was performed, and a return toward the principles initially established by Gibbon (figure 1). The screens used are shorter than those originally described by Gibbon, as 85 per cent of oxygenation in the vertical screen-oxygenator occurs in the first 25 cm. of screen height. Following a suggestion by Dr. Lewis Bosher, we found that oxygenation is improved when the recirculation rate through the oxygenator is increased; this is probably simply because of more trips of the blood over the screen. The recirculation rate usually is about 200 ml. per screen, and at this rate approximately 10 ml. of oxygen can be added per screen per minute.

The apparatus is automatic in the sense that a nearly constant volume of blood is contained in the machine, venous inflow being accurately balanced electronically by arterial return to the patient. Similarly, blood scavenged from

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the heart and pericardium during the bypass is automatically returned to the circulation.

A sliding mechanical filmer is used which abolishes the need for filling the oxygenator with saline and the accompanying dilution of the priming blood. Eight screen and 20 screen oxygenators are interchangeable and allow oxygenation of 1600 and 4000 ml. of blood and require 2000 and 2900 ml. as priming volumes. In each instance after the oxygenator is filmed, about 200 ml. of blood can be returned to the reservoir for transfusion during the bypass.

A good scavenging system for removal of blood within the heart is imperative, particularly in treating patients with tetralogy of Fallot and a large bronchial blood flow; this anomaly currently represents about one-third of our cases. Gentle suction regulated to a maximum of 22 mm. Hg and siphon drainage to a level approximately 60 cm. below the usual right atrial position are used for scavenging blood about the heart during bypass. When flow is extremely high, ⅜ in. tubing is used for the scavenging suction, but usually a tubing with an inside diameter of ¼ in. suffices. Three scavenging suction lines are used which lead into a common chamber containing a plastic sponge coated with antifoam, from which the blood is automatically returned to the circulation.

The capacity of the apparatus is limited to the addition of about 200 ml. of oxygen per minute. Unless this rate is exceeded, the arterial saturations are regularly above 92 per cent. If an unusually large person is operated on, the Harrison-Brown heat exchanger may be incorporated into the circuit and the body temperature lowered. However, we have never recognized difficulty from arterial oxygen saturation even as low as 60 to 70 per cent provided the blood flow is well maintained. Arterial saturations as low as 60 to 70 per cent occasionally were obtained with earlier, smaller, less efficient apparatus, and occur at present in an occasional case of tetralogy of Fallot when the bypass is initiated.

Adequacy of mechanical respiration and blood flow can be judged best from the arterial pH, which rarely falls more than a tenth of a pH unit below normal. In the absence of cardiac or respiratory insufficiency, acidosis has not occurred postoperatively. Free plasma hemoglobin has not risen alarmingly even in adult patients with tetralogy of Fallot in whom a large portion of the arterial return is removed from the heart with the scavenging suction. The level of free plasma hemoglobin only reflects hemolysis and does not quantitate it accurately as the patient continually removes hemoglobin from the blood. Dangerous levels have not been observed.

After use, the disassembled parts are washed with water and a detergent and soaked for 30 minutes in a 20 per cent solution of sodium hydroxide before being rinsed with tap water, dried and reassembled. Sterilization by exposure to ethylene oxide has been reliable and effective.

A more complete description of the apparatus has been published recently.[2]

Conduct of Bypass

Anesthesia is induced with nitrous oxide, succinylcholine, PENTOTHAL® or FLUOTHANE®. The patient often moves quietly during the operation. We avoid entry into either pleural cavity in most cases with a median sternotomy, and with better control of bleeding we have in most instances avoided creating a window into the right pleural cavity at the completion of the procedure. Cardiac tamponade is perhaps a little more likely to occur if such a pericardial window is not opened, and increased vigilance for this is necessary. There seems, however, to be less bleeding when the additional dissection for creation of the window is not done.

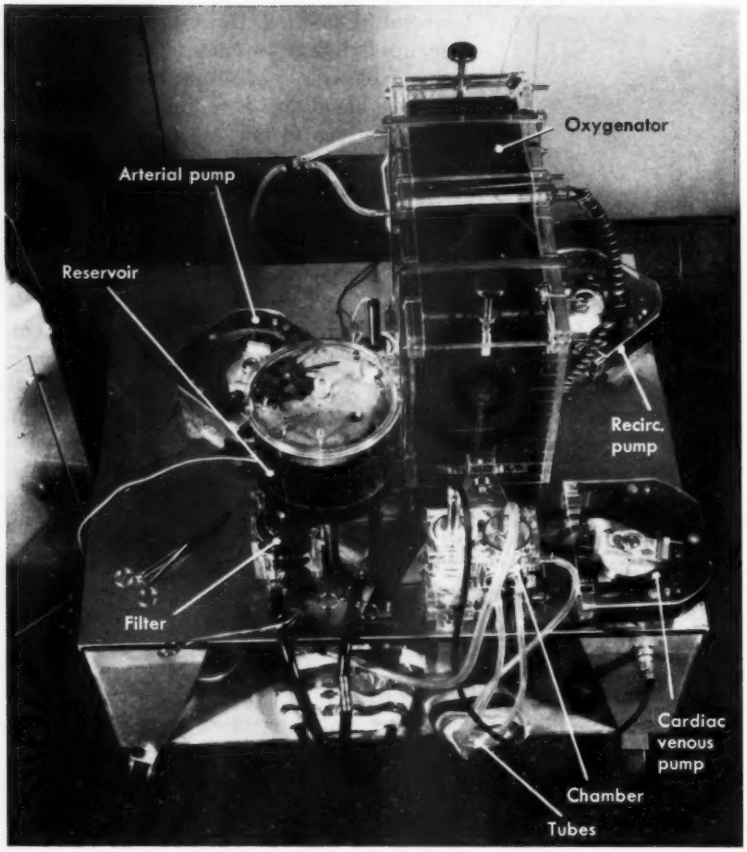

FIGURE 1. Pump-oxygenator in current use. Electric controls for pumps are housed in a separate mobile console.

Heparin is given in a dosage of 3 mg. per kilogram of body weight, and the pump is primed with blood (drawn the morning of operation from matched donors) to which has been added 20 mg. of heparin for each 500 ml. of blood. The dangers of too little heparin and of thrombosis are more to be feared than the danger of too much heparin, as one can neutralize the drug with POLYBRENE® at the completion of the bypass. Careful studies have demonstrated inactivation of heparin during the bypass, so that we give an additional milligram per kilogram of body weight after the first 30 minutes of bypass, and 0.5 mg. per kilogram after each additional 30 minutes. At the completion of the bypass, this heparin is neutralized with Polybrene, milligram for milligram, and an additional dose of half this amount of Polybrene is given 10 minutes later. This regimen almost invariably is associated with a return of clotting time to normal within 10 minutes.

We continue to monitor aortic and inferior vena caval pressures by direct cannulation, but with increased experience we have had less need for monitoring. Careful monitoring of the electrocardiogram, as well as the visible cardiac action, is helpful during stitching in critical areas, and this has helped us avoid production of permanent heart block by removal of an offending suture in patients with a ventricular septal defect.

In many instances, continued cardiac activity and the presence of significant quantities of blood in the heart obscure the operative area to such an extent that suturing is

TABLE 1

SURVIVAL RATES FOR INTRACARDIAC OPERATIONS

LESION	FIRST 300 CASES		LAST 100 CASES	
	Number	*Survival rate (per cent)*	*Number*	*Survival rate (per cent)*
Aortic stenosis				
Congenital	36	86	9	100
Adult	20	40	1	0
Aortic insufficiency	5	60	2	50
Ventricular septal defect	105	75	29	93
Tetralogy of Fallot	55	74	31	68
Mitral insufficiency	11	36	3	0
Mitral stenosis	6	100	1	100
Pulmonary stenosis, intact ventricular septum	12	75	4	100
Atrial septal defect				
Secundum	13	92	7	100
Primum	15	60	10	80
Anomalies of pulmonary veins	6	83		
Aneurysm of aortic arch	9	45	2	100
Miscellaneous	7	57	1	0

difficult. Under such circumstances, we occlude the aorta for periods ranging up to five minutes, but we follow such periods with at least a minute of resumed coronary flow. During this period of ischemia, the heart usually slows but it rarely stops, and the arrhythmia improves rapidly when circulation is restored. Hypothermia has been used in a few instances in recent experience. This has been valuable in patients with tetralogy of Fallot and a previous aortic-pulmonary anastomosis, in whom, after cooling to around 20° C., the bypass can be temporarily stopped, the pulmonary artery opened, and the Potts anastomosis sutured from inside the pulmonary artery. A lesser degree of hypothermia, around 26 to 28° C., frequently is used in patients with aortic valvular disease to minimize coronary flow requirement. In such patients, when the coronary flow must be interrupted for longer than 10 to 12 minutes, perfusion of oxygenated blood is given intermittently into the coronary orifices.

Discussion of Cases

Table 1 summarizes the survival rates in the last 100 cases as well as in the first 300 intracardiac operations. For most conditions, operative survival has improved, but a true picture of the operative risk in typical and straightforward cases and the reasons for our confidence in the effectiveness of cardiopulmonary bypass can be gained only by more detailed study. In our early experience, only the most severely ill patients were operated on, and some of them would, at present, be considered inoperable. Recently, better-risk patients have been treated, but those who are desperately ill and in need of correction are not excluded. A brief discussion of the individual lesions, indications for operation, and fundamentals of treatment follows.

Aortic stenosis—Congenital aortic stenosis and its treatment have been discussed fully in a recent report.[3] The results have been gratifying, 38 of 40 patients with uncomplicated valvular or subvalvular stenosis surviving operation with a decrease in the aortic gradient and improvement in the clinical picture. The greatest problem in such patients is subvalvular stenosis, which in many instances may be extremely tight. Great care is necessary to avoid damage to the mitral valve or ventricular septum when the subvalvular scar tissue is excised.

In the adult, the stenotic aortic valve frequently is severely calcified and resembles a bed of coral. In a number of instances the calcified material can be removed from the valve and an adequately functioning leaflet

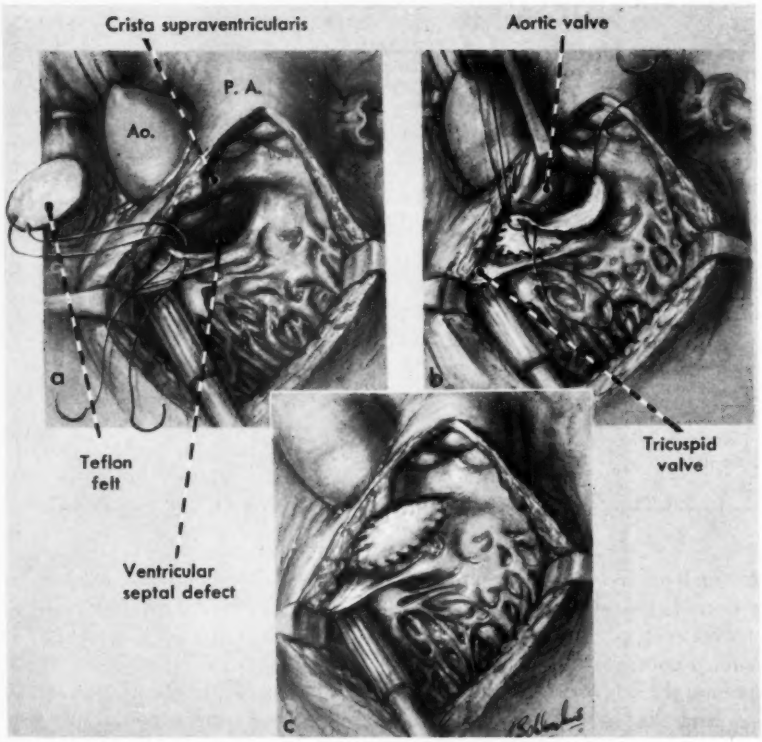

FIGURE 2. Repair of ventricular septal defect.

a. A double-arm 3-0 silk suture is begun posteriorly, care being taken to grasp only the fibrous tissue in this area. The aorta is occluded temporarily.

b. The aortic valve must be seen clearly and avoided, as it is easily torn. Bites on the muscular septum caudally are taken mostly on the right side.

c. Completed repair.

obtained, but little can be accomplished with such valves unless adequate time is available for meticulous work on the leaflets. A combination of moderate hypothermia (28 to 30° C.) and intermittent or continuous perfusion of the coronary arteries allows such time. We are convinced that perfusion of both coronary arteries is preferable to perfusion of either alone. None of the methods used for coronary perfusion has been entirely satisfactory, and we use various combinations of small balloon-tipped catheters placed directly in the coronary orifices and held in place with a purse-string suture, and ball-tipped metal cannulas which are held manually against the artery. Great care must be taken to remove bits of calcium which break off from the valve; a sponge placed into the ventricle aids in catching these. In instances in which a leaflet is irreparably damaged in the removal of the calcified material or aortic insufficiency results from the destruction of a leaflet by bacterial endocarditis or rheumatic fever, the use of TEFLON® aortic leaflets has given gratifying results. Five of eight patients so treated are alive and considerably improved; several have normal blood pressure.

To some extent, the high mortality rate among adults with aortic stenosis may be due to inadequate attention to venting of the left

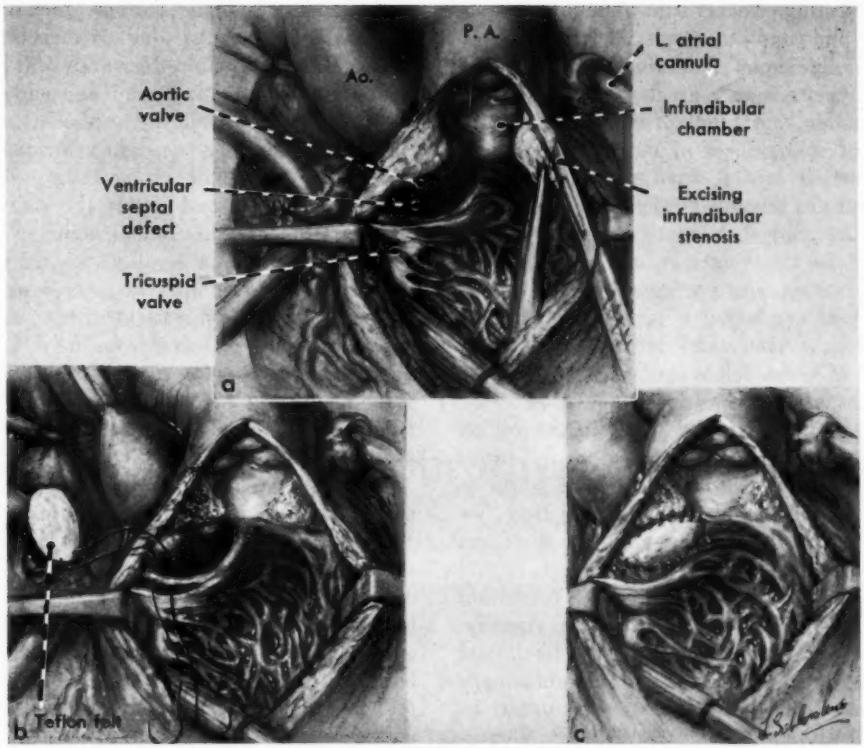

FIGURE 3. Repair of tetralogy of Fallot. The hypertrophied and scarred crista supraventricularis is cut away and the ventricular defect is repaired as shown in figure 2. If the right ventricular outflow tract, pulmonary artery or valve ring offers obstruction due to small size, a patch of Teflon fabric is used to enlarge the area.

ventricle in the period before cardiac action effectively returns. Recent experience in cases in which the left ventricular blood was aspirated and the volume estimated indicates that this volume may be tremendous in patients with only moderate insufficiency. Overdistention of the ventricle may be difficult to recognize, as the distended, hypertrophied heart often does not feel very different from the hypertrophied heart without distention. Use of a large vent directly into the left ventricle is advisable in such cases.

Ventricular septal defect—This lesion is commonly treated and accounts for about one-fourth to one-third of the total cases. If infants weighing less than 25 lb. and one patient with severe aortic insufficiency and failure are excluded, only two deaths have occurred among the last 50 patients in whom a ventricular septal defect has been closed surgically. Both of these patients had severe pulmonary hypertension, and in one a postoperative mediastinitis developed. From our results it appears that the risk of closure of ventricular septal defect is little more than that of interruption of a patent ductus arteriosus, and most patients with a functionally important lesion should be operated on.

We have temporarily stopped attempting to close ventricular septal defects in infants who have cardiac failure, as the risk is prohibitive at the present time. In most infants without other complicating lesions, the failure can be treated and the child's condition improved. Some of them have been treated by banding of the pulmonary artery, anticipating correction at a later date. One patient so treated has had successful closure of the defect.

In selecting patients with pulmonary hypertension and ventricular septal defect for operation, the likelihood of survival and subsidence of the hypertension is greater if there is roentgenographic and electrocardiographic evidence of enlargement of the left atrium and left ventricle and if cardiac catheterization demonstrates increased pulmonary blood flow. When the clinical evidence suggests that the work of the two ventricles and the resistance of the two circuits are approximately equal, the risk of correction is prohibitive.

Unless the ventricular defect is quite small, a patch of Teflon felt is used to close it (figure 2). This is sutured with 3-0 silk around the periphery, being careful to avoid the region of the conducting bundle in the posterior angle of the defect. Although the aorta is intermittently occluded during this time, we prefer to have the heart beating so that a heart block is immediately apparent.

Tetralogy of Fallot—The risk of correction of tetralogy of Fallot has diminished steadily. Because of the low risk and great likelihood of improvement after a subclavian-pulmonary anastomosis in young patients in contrast to a relatively high mortality rate when correction is attempted in this age group, we use the anastomotic procedure for patients up to the age of about six years. As a consequence, most of the patients operated on for correction of tetralogy of Fallot have had previous procedures, some as many as three operations before correction was possible. Previous subclavian-pulmonary anastomoses do not seem to add significantly to the operative risk.

Recently we have become more aware of complications related to the coronary arteries in patients with tetralogy. A common anomaly is origin of the anterior descending artery from the right coronary. In such instances the vessel goes across the outflow tract and the line of the usual ventriculotomy incision; division of this vessel almost certainly will lead to death. In other instances an unusually large branch may arise from the normal right coronary artery but cross the right ventricular outflow tract to become an accessory anterior descending artery and supply the ventricular septum; this has, in some instances, almost certainly been the cause of a low cardiac output after operation and an otherwise unexplained death. In one patient with an anterior descending artery arising from the right coronary, atriotomy was performed, the tricuspid valve detached, and the defect readily closed from above. Perhaps this approach should be used more frequently.

It is imperative that both infundibular and pulmonary valvular obstructions be relieved. Wide excision of the infundibular muscle and scar usually can be done and an adequate opening obtained (figure 3). In some instances the pulmonary valve and adjacent artery are small and a patch must be inserted for enlargement. This has been done more frequently in recent experience, and approximately half the patients have had patches inserted. A piece of Teflon aortic prosthesis has worked most satisfactorily.

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The Role of the Urologist in the Diagnosis and Treatment of Pseudohermaphroditism

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Some principles governing the diagnosis and the medical and surgical treatment of male and female pseudohermaphroditism are presented.

The urologist consulted concerning an individual who exhibits some form of abnormal sex differentiation faces the following problems: differential diagnosis between female pseudohermaphroditism with congenital adrenal hyperplasia and other types of hermaphroditism, selection of the sex of rearing in the absence of adrenal hyperplasia, psychologic management of patient and parents, application of surgical procedures, and use of sex hormones at puberty.

WILLIAM W. SCOTT

WHEN a urologist is asked to determine the sex of an infant who exhibits some form of abnormal sex differentiation and to conduct any operative procedures necessary so that the external genitalia will conform with the sex of rearing, he is indeed fortunate if he is able to consult with a pediatrician who specializes in endocrine disorders. Even when this problem appears simple, it may be quite complex, and time is of the essence. Most urologists and even most pediatricians cannot expect to keep abreast of the rapid developments in the field of pediatric urology and hence must rely on specialists in this field. I place myself in the category of "most urologists," and on almost every occasion when I have been confronted with a problem in abnormal sex differentiation I have consulted Dr. Lawson Wilkins, professor of pediatrics at The Johns Hopkins Hospital, or one of his group.

I shall present in simplified form a few principles which govern the diagnosis and treatment of male and female pseudohermaphroditism. Principles governing the diagnosis and medical management have been

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gleaned largely from Wilkins and his associates; principles governing surgical management are those of a number of surgeons and urologists and are acknowledged as they are presented. Space does not permit a comprehensive coverage here, and the interested reader is referred to chapters and texts on the subject.[1,2] For example, the chapter on the fascinating subject of embryonal sexual differentiation in the book by Jones and Scott,[2] written by Alfred Jost, professor of comparative physiology, Faculty of Sciences, University of Paris, is a most informative, comprehensive, up-to-date account.

Although the etiology of various types of abnormal sex differentiation is a complicated subject, fortunately the problems the urologist faces in deciding the sex and rearing and the treatment of a pseudohermaphrodite are relatively simple. They are (1) the differential diagnosis between a female pseudohermaphrodite with congenital virilizing adrenal hyperplasia and an individual with another type of hermaphroditism, (2) selection of the sex of rearing if the patient does not have adrenal hyperplasia, (3) psychologic management of the patient and the parents, (4) application of surgical procedures to adapt the patient as well as possible to the gender role selected, and (5) the use of sex hormones at puberty if they are indicated.

Female Pseudohermaphroditism With Congenital Adrenal Hyperplasia

It must be stressed at the outset that female pseudohermaphroditism with adrenal hyperplasia must be distinguished from other forms of pseudohermaphroditism, because the treatment differs considerably and the sex of rearing should always be female. As in female pseudohermaphroditism without adrenal hyperplasia, the external genitalia may be partially masculinized, but the genital ducts and gonads are entirely female. The phallus is enlarged, but the external genitalia may vary appreciably depending on the degree of fusion of the labioscrotal folds. There may be separate vaginal and urethral openings, a urogenital sinus or even a phallic urethra. Such changes are considered to be caused by excessive secretion of androgen by the adrenal cortices of the fetus.

A first step in the differential diagnosis of female pseudohermaphroditism with adrenal hyperplasia and other forms of pseudohermaphroditism can be the determination of the sex chromatin pattern. In 1953, Barr[3] and associates demonstrated for the first time a sex difference in the pattern of the nucleus of certain somatic cells. These original studies were made on skin, but it has since been shown that such differences are demonstrable in properly prepared specimens of testes, ovaries, breast, polymorphonuclear neutrophils, and buccal and transitional epithelium. At present, most workers prefer smears prepared from buccal scrapings. In these preparations, nuclei of normal females and female pseudohermaphrodites show a distinctive large clump of chromatin just beneath the nuclear membrane which takes a metachromatic stain. This clump of chromatin is not present in the nuclei of cells from normal males or male pseudohermaphrodites. Thus it is easily possible in most instances to determine by buccal smear the gonadal sex of the individual, regardless of the appearance of the external genitalia. Exceptions may include a small percentage of newborn infants who have normal genitalia and unusual conditions such as Klinefelter's syndrome.

A second step in the differential diagnosis can be determination of the 24 hour output of total urinary 17-ketosteroids. Normally, prior to puberty, values for total urinary 17-ketosteroids are very low (less than 1 mg. per day) and pregnanetriol is not present in the urine. If the value for urinary 17-ketosteroids is elevated or if pregnanetriol is present in the urine of an infant or a child whose sex chromatin pattern is female, such a patient should be raised as a female. If masculinization of some degree has been present since birth or appeared shortly thereafter, such a child almost surely is a female pseudohermaphrodite with congenital adrenal hyperplasia and, as Lawson Wilkins has shown, is best treated with cortisone in a dosage regulated so that urinary 17-ketosteroids are normal to low-normal.

Female pseudohermaphrodites with adrenal hyperplasia are thus distinguished from female pseudohermaphrodites without adrenal hyperplasia and from male pseudohermaphrodites. Of course, virilization in the female can occur almost anytime postnatally, secondary to excessive production of androgen by hyperplastic adrenals or a masculinizing adrenal tumor. However, in postnatal adrenal hyperplasia and in adrenal tumor the secondary sex characters are normal at birth. Usually a tumor can be distinguished from hyperplasia on the basis of the response of the urinary 17-ketosteroids to administration of cortisone. In the presence of a tumor, these levels will remain unchanged; in the presence of adrenal hyperplasia, they will fall.

Selection of Sex of Rearing in Pseudohermaphroditism Without Congenital Adrenal Hyperplasia

If one excludes female pseudohermaphroditism with congenital adrenal hyperplasia, considerable confusion still exists concerning the sex of rearing of infants with other forms of intersexuality. We agree wholeheartedly with Wilkins that in male pseudohermaphroditism and in true hermaphroditism a decision regarding the sex of rearing should be based on the size of the phallus or the presence of an adequate vagina, without regard to the structure of the internal genital tract, chromosomal pattern, or type of gonad. In other words, a male pseudohermaphrodite or a true hermaphrodite exhibiting a large phallus—one which we urologists could make into a respectable penis—should be raised as a male. A male pseudohermaphrodite or a true hermaphrodite exhibiting the opposite finding, an adequate vagina and a tiny phallus, should be raised as a female.

Wilkins makes an exception to the rule of selecting the sex of rearing according to the anatomy of the external genitalia in the rare instances of female pseudohermaphroditism without adrenal hyperplasia, provided this diagnosis is established in infancy. If the diagnosis is established in infancy, the phallus should be excised and the urogenital sinus corrected to form a separate vagina and urethra. The ovaries of such children mature at puberty, and menstruation and ovulation will occur.

Psychologic Management

The psychologic management of these children and their parents is most important. In cases of intersexuality in which the external genitalia are ambiguous, the physician often refuses to make a definite decision and postpones diagnostic procedures until later life, thus leaving patient and parents in a confused state and often mentally distraught.

Psychologic studies made in our hospital by Money, Hampson and Hampson[4] indicate strongly that any decision regarding the sex of rearing should be made before the age of two years. They have found that a change in the sex of rearing after two years of age, except for rare exceptions of postadolescent requests for change of sex, may be psychologically disastrous. Consequently, after the age of two years, even in instances in which the original selection of the sex of rearing was incorrect, a change should not be made. Rather, these children should receive hormonal and surgical therapy directed toward helping them to conform as closely as possible to the sex in which they are being reared.

If a patient already has reached maturity, there should be no dogmatic objection to voluntary requests for change to the opposite sex if it is more compatible with the external genitalia.

Surgical Procedures

Often we must apply surgical procedures to adapt the patient as well as possible to the gender role selected. As urologists, we are much more apt to be asked to construct masculine external genitalia in a male pseudohermaphrodite or a true hermaphrodite with a large phallus, leaving the construction of female external genitalia to the gynecologists.

The surgical procedures that may be required in construction of masculine genitalia are laparotomy for excision of contradictory structures, straightening and lengthening of the phallus, construction of a urethra, approximation of the two halves of the labia or scro-

tum, orchiopexy, insertion of artificial testes, and excision of breasts.

It has been our policy to excise internal female structures first. This is done at an early age, and at the same time the phallus is straightened and lengthened. In dealing with a true hermaphrodite, at laparotomy the ovary is removed and the testis allowed to remain; in a male pseudohermaphrodite, the testes are merely inspected, because extensive manipulation, dissection or biopsy will prevent delayed spontaneous descent.

If a vagina or a vaginal pouch has been demonstrated, it is wise to allow it to remain until the time when a urethra is constructed. At times, vaginal epithelium serves admirably as a free tunnel graft in urethral construction.

Urethroplasty often can be accomplished before school age, and in recent years we have preferred the method of Denis Browne.[5] However, we prefer to use vertical mattress sutures over rubber catheter stops rather than single deep sutures affixed at each end with glass and metal stops, because we have found that the latter often cut through the skin and cause fistulas.

Approximation of the two halves of a bifid scrotum or the labia majora is best done at the time of urethroplasty unless a tunnel graft is used which requires anastomosis to the old urethra.

At times, both gonads are found well down in the scrotum or labia and remain at this level. If they are cryptorchid, we have delayed orchiopexy until puberty, and prefer the method of Robert Gross[6] to that of Torek.

If bilateral testicular atrophy is found, it may be necessary to insert artificial testes. We have found VITALLIUM® prostheses to be nonreactive. These are best inserted into the scrotum through a low inguinal incision placed so that the line of closure of the skin is considerably above the final resting place of the prosthesis. In our experience, none of these prostheses have sloughed. Only one wound has required secondary closure, and in this instance the Vitallium testis was inserted through a scrotal incision. At present we are contemplating making artificial testes out of SILICONE® rubber.

Male pseudohermaphrodites occasionally will feminize at puberty, and if raised as males it may be necessary to perform plastic mastectomy. Pseudohermaphrodites who have internal genital structures that are predominantly female usually masculinize, while those with only vestiges of internal female organs may either masculinize or feminize.

Use of Sex Hormones at Puberty

Whenever the gonads of an infant with some form of intersexuality are removed, it is very important to trace these children through puberty. At times it may be necessary to administer androgenic or estrogenic hormones, according to the sex of rearing.

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Anterolateral Chordotomy for Relief of Pain

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Among the factors which have been cited as influencing the success or failure of chordotomy are the disease responsible for the pain, addiction to drugs, duration of pain, neurosis, organic neurologic involvement, localization of the pain, the type of anesthesia, and the depth of the operative incision. An analysis of the results of chordotomy in 121 patients is presented which considers these and other aspects of the operation. Chordotomy relieved the pain completely in 67 per cent of the cases, produced a fair result in 21 per cent, and failed in 7 per cent.

ONE of the oldest problems for physicians is the relief of pain. Removal of the cause, the best solution, is not always possible. When the cause cannot be eliminated directly, as in metastatic tumors, causalgias, phantom limbs, etc., the pain itself is the major problem. A complicating factor is the emotional reaction of the patient, which may assume more serious proportions than the primary pain and present a formidable therapeutic problem.

HANS ERICH DIEMATH

Anterolateral chordotomy is by far the most common neurologic surgical procedure used to relieve pain in the limbs and body. We shall attempt to analyze the reasons why anterolateral chordotomy relieves pain completely in some instances but fails to do so in others.

Material

This report is based on a review of 126 cases (63 men, 63 women) in which a total of 148 chordotomies were performed for the relief of intractable pain. Ninety-six of the operations (79 patients) were performed at The Johns Hopkins Hospital† in the past 10 years, and 52 of the operations (47 patients)

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were performed at the Chirurgische Universitätsklinik, Graz, Austria, in the past seven years. The analysis of the results includes only 121 of the 126 patients, because the records of five patients (four men, one woman) were either unavailable or inadequate.

In the majority of the cases, chordotomy was performed in the upper thoracic region, and approximately half of the operations were unilateral (table 1). Eight patients had bilateral chordotomy in two stages (two cervical, six thoracic). Apparently the criteria for selection of patients for a one-sided operation were satisfactory, for the results of the unilateral operations and of the bilateral operations were the same.

Early Postoperative Results

The early postoperative results are defined in terms of the subjective relief from the original pain in the first two weeks after operation (table 1). The scores are based on the total group, including the patients dying shortly after operation. Using these criteria, 67 per cent of all the patients had complete relief of pain (69 per cent of those having primary chordotomy; 46 per cent of those having secondary chordotomy). If the calculation is based on survivors only, we find that 70 per cent of all the patients and 72 per cent of the patients having primary chordotomy had complete relief of pain. Grant[1] reported that 64 per cent of the patients in his series had complete relief of pain following chordotomy, and White and Sweet[2] reported a figure of 81 per cent. The percentage of failures in White and Sweet's series was almost the same as it was in our series (10 and 7 per cent, respectively).

Factors Influencing the Results of Chordotomy

Although Wolff and Wolf[3] expressed the belief that the "pain threshold" is consistent from person to person and in the same person at different times, Hollander[4] reported that the threshold for reaction to pain in American Indians, Negroes and prize fighters is different from the threshold in white persons living in urban areas. Since both the threshold and the reaction to pain are important factors in clinical problems, they cannot be dissociated in assessing results.[5-7] That pain is a problem among peoples of all races and social levels is attested by many lines of evidence; one that might be cited is Rasmussen and Freedman's[8] report on severe causalgia in Chinese peasant soldiers.

Sex—The number of men and women in our series was identical. This probably indicates that there is little difference in the appreciation of pain or in the degree of medicinal relief between the sexes, assuming that the etiologic conditions are similar. The early postoperative results were not quite the same in men and in women; 36 of 59 men (61 per cent) and 45 of 62 women (73 per cent) obtained complete relief of pain following chordotomy. However, this difference is not statistically significant, and this is confirmed by the almost identical number of failures in men and in women.

Race—Of the relatively small group of nonwhite patients (14), the percentage who obtained complete relief (93 per cent) was higher than it was among the white patients (64 per cent). The nonwhite group included a somewhat higher proportion of women than the white group, and this may be a factor in the better results.

Cause of pain—The diseases responsible for the intractable pain were largely neoplastic; 88 (73 per cent) of the 121 patients had malignant tumors (table 2). Most types of neoplasm are represented, with carcinoma of the cervix being the most common (29 cases). Although the series is small, the results of chordotomy in patients with carcinoma of the cervix are somewhat better than the results in

TABLE 1

EARLY POSTOPERATIVE RESULTS OF ANTEROLATERAL CHORDOTOMY

TYPE OF CHORDOTOMY	NUMBER OF PATIENTS	DEGREE OF RELIEF			PATIENTS DEAD OR DISABLED
		Complete	*Fair*	*None*	
Primary					
Cervical, unilateral	23	16	6		1
Cervical, bilateral	6	3 (69%)	1 (19%)	1 (7%)	1 (5%)
Thoracic, unilateral	38	26	4	6	2
Thoracic, bilateral	43	31	10	1	1
Secondary	11	5 (46%)	4 (36%)	1 (9%)	1 (9%)
TOTAL	121	81 (67%)	25 (21%)	9 (7%)	6 (5%)

the patients having other types of neoplasm.

In the non-neoplastic group, made up mainly of patients with tabes dorsalis, phantom limb, intercostal neuralgia and trauma of the spine, the results of chordotomy are generally good. Two patients had abdominal aneurysm and obtained relief of pain. Two had neurofibromatosis; one obtained relief and one did not. There was one case each of postherpetic neuralgia, vascular myelopathy, Perthes' disease, severe lumbar spondylosis, vascular gangrene of an extremity, and tabes dorsalis; each of these patients obtained complete relief of pain. One patient had severe pain in the hip which was not improved following chordotomy, and one had a painful irradiation scar and obtained only partial relief.

The question has been raised whether the results of chordotomy are as good in the presence of malignancy as in nonlethal conditions. In this series, 59 of the 88 patients with malignant lesions (67 per cent) had complete relief of pain, and 22 of 33 patients with nonneoplastic conditions (also 67 per cent) had complete relief of pain following chordotomy. Thus, there would seem to be no difference in the early postoperative results in these two groups. However, we should mention that all but two of the patients who died as a result of the chordotomy or were severely disabled were patients with malignant tumors. The number of failures was about the same in the two groups.

Addiction and duration of pain—Many writers have said that addiction tends to lower the percentage of beneficial results of chordotomy. In this series there is no appreciable difference in benefit between the addicted patients and the nonaddicted patients (table 3), although the number of failures in the addicted group is considerably higher. An analysis of the early postoperative results based on the duration of pain prior to chordotomy is presented in table 4.

Neurosis—It is well known that severe and persistent pain can break the morale of even the most stable person. Neurotic reactions related to compensation, desire for sympathy, etc., may occur in any patient.[2,9,10] For this reason, some surgeons[2,11,12] have suggested that a preliminary block should be used to determine whether or not relief of pain may be obtained. It is admitted that spinal blocks are not reliable indicators of the result of chordotomy. A differential spinal block[13] or a chronic epidural block may be more reliable. In this series, nine patients had alcoholic injections into nerves prior to chordotomy. Although these procedures were not employed primarily as therapeutic tests, they may be analyzed as such. A 24 year old white man obtained relief of pain following a caudal block, and subsequent chordotomy gave permanent relief. A 68 year old man was not relieved of pain by injection of alcohol in an intercostal nerve (for neuralgia secondary to thoracoplasty for pulmonary tuberculosis); a left cervical chordotomy at the level of C5 gave complete relief temporarily, but the pain recurred in one month. Of the six patients who had primary relief following alcohol injections, chordotomy produced complete relief

TABLE 2

RESULTS OF CHORDOTOMY FOR NEOPLASTIC AND FOR NON-NEOPLASTIC CONDITIONS

CONDITION	NUMBER OF PATIENTS	DEGREE OF RELIEF			PATIENTS DEAD OR DISABLED
		Complete	*Fair*	*None*	
Neoplastic					
Carcinoma					
Cervix	29	24	1	3	1
Rectum	10	7	2	1	
Lung	8	3	4		1
Prostate	7	4	2	1	
Breast	5	4	1		
Bladder	4		1	1	2
Sarcoma	6	3	3		
Hodgkin's disease	3	2	1		
Miscellaneous neoplasms	9	7	2		
Primary site unknown	7	5	2		
Non-neoplastic					
Gastric crises	4	3	1		
Phantom limb	5	3			2
Trauma of spine	5	2	2	1	
Intercostal neuralgia	4	3	1		
Arachnoiditis	3	2	1		
Miscellaneous	12	9	1	2	
TOTAL	121	81	25	9	6

of pain in five and improvement in one. Of two patients in whom alcohol injections did not relieve the pain, chordotomy produced complete relief in one and no relief in one. Nine patients were operated on in spite of the fact that each of them was recognized to have a neurosis. The early postoperative results in this group were surprisingly good. Eight patients had complete relief of pain, and only one failed to benefit. However, four of these eight patients had recurrence of pain within a few weeks. All these neurotic patients had had pain for a long time before operation (average, four and three-fourths years).

Organic neurologic involvement—Of 40 patients having clinical evidence of peripheral neurologic involvement, 28 (70 per cent) were completely relieved of their pain by chordotomy and only three (7.5 per cent) did not obtain relief; one patient died shortly after operation. It would seem that the results of chordotomy are not influenced significantly by the presence of organic neurologic involvement. This is of particular importance, since it is now believed that pain due to involvement of a plexus and peripheral nerve is unlikely to be affected either by lobotomy or by thalamotomy.

Ambulatory state—Patients who had malignant tumors and were bedridden seemed to do about as well as other patients. Although narcotics did not control their pain before operation, seven of 11 patients had complete relief after chordotomy. One patient who died shortly after the operative procedure did not seem to be helped at all.

Localization of the pain—The region of the body involved by pain has been considered a factor in the outlook following chordotomy. In this series, 14 of 21 patients (66.6 per cent) with pain in the shoulder and arm had complete relief, whereas only 58 per cent of patients with pain in other parts of the body obtained such benefit (table 5). Patients with sacral, perineal or perianal pain did quite well following chordotomy, although unilateral section did not give good results; this is not necessarily due to sacral sparing, which was not consistently present following performance of unilateral chordotomy.

Degree of analgesia—Some neurosurgeons believe that local anesthesia should be used

TABLE 3

EFFECT OF ADDICTION ON RESULTS OF CHORDOTOMY

STATUS	NUMBER OF PATIENTS	DEGREE OF RELIEF			PATIENTS DEAD OR DISABLED
		Complete	*Fair*	*None*	
Addicted	23	16 (69%)	2 (9%)	5 (22%)	
Not addicted	98	65 (66%)	23 (24%)	4 (4%)	6 (6%)

TABLE 4

RELATION BETWEEN DURATION OF PAIN AND EARLY POSTOPERATIVE RESULTS

PREOPERATIVE DURATION OF PAIN	NUMBER OF PATIENTS	DEGREE OF RELIEF			PATIENTS DEAD OR DISABLED
		Complete	*Fair*	*None*	
Six months or less	12	9 (75%)	2 (17%)	1 (8%)	
Six months to one year	36	26 (72%)	6 (17%)	3 (8%)	1 (3%)
More than one year	48	33 (69%)	11 (23%)	3 (6%)	1 (2%)

for chordotomy so that the patient may cooperate in testing for the sensory level. It is recognized that an adequate level at the time of operation may fall many dermatomes in the succeeding weeks with or without return of the original pain. Further, even if the level does not fall appreciably, the pain may return. One patient, after unilateral chordotomy at C2, had complete relief of pain without any demonstrable sensory loss over the opposite side. This is the exception rather than the rule, however, and usually if the appreciation of pinprick returns the pain comes back. But complete relief of pain may occur in patients who have only a hypalgesia.[14] Grant and Wood[15] concluded that anatomic complete sections of the spinothalamic tract are obtained more frequently than symptomatic good results, except in high cervical chordotomies, in which instances these authors believe the two are about equal in frequency. That a complete loss of pinprick may be present in a painful area may be illustrated by a patient who, after a unilateral thoracic chordotomy, had an analgesia to the level of D7 but still experienced severe pain in the hip. Such pain may be due to ipsilateral innervation[16] of the part, which presumably occurs in about 10 per cent of patients.

Anesthesia for operation—It is difficult to draw conclusions regarding the advantage of local anesthesia in the present series. Only one of the neurosurgeons (A.E.W.) has used local anesthesia routinely. It was used in 30 operations in 21 patients. Comparison of this group with the group in which general anesthesia was used reveals that the percentage of patients having relief of pain was about the same, namely, 69 to 70 per cent, but 80 per cent of the patients operated on under local anesthesia had an adequate level of analgesia compared with only 62 per cent of the patients operated on under general anesthesia. If we examine the results of only the operations performed by the neurosurgeon who routinely has used local anesthesia, we find that 87 per cent of the patients had complete relief of pain and 94 per cent had adequate levels of analgesia one month after operation. These figures probably indicate that in the hands of a surgeon accustomed to using local anesthesia for chordotomy a somewhat better result may be obtained than if general anesthesia is used. We have not found the technic used by White and Sweet[2] of awakening patients during the course of the operation to test the sensory level to be satisfactory, as most patients do not recover sufficiently to cooperate well.

TABLE 5

RELATION BETWEEN LOCATION OF PAIN AND RESULTS OF CHORDOTOMY

LOCATION OF PAIN	NUMBER OF PATIENTS	TYPE OF CHORDOTOMY				DEGREE OF PAIN RELIEF		
		Cervical		*Thoracic*		*Complete*	*Fair*	*None*†
		Unilateral	Bilateral	Unilateral	Bilateral			
Shoulder	8	7			1	5	3	
Chest	13	8	1	1	3	7	5	
Upper extremity*	13	12			1	9	4	
Abdomen and pelvis	18		4	4	10	11	6	1
Back	41	1	1	17	22	29	7	4
Hip	35	1	4	12	18	23	9	3
Thigh, calf, foot	74	3	4	32	35	53	13	7
Sacral, perineal, perianal	21		2	3	16	15	6	

*Excluding cases of phantom limb pain.

†Three deaths not included.

Depth of the incision—The depth of the incision as described by the surgeons has not correlated well with degree and extent of sensory loss. This discrepancy may be due to several factors. The surgeon is not always certain of the depth and direction of the incision, and secondary vascular disturbances may produce large lesions. In one patient, a cut 3 mm. deep at C3 on the left side and at C1 on the right side produced an analgesia below T3 with a patchy hypalgesia above this level on the right but little if any impairment of sensation on the left (although the patient had transient urinary retention and weakness of both legs). It is possible that these differences in results from the same type of incision to the same depth in the same part of the spinal cord may simply indicate that there are marked individual variations in the intraspinal position of the spinothalamic tract.[17]

Electric stimulation of the spinal tracts was used in only one patient. It was believed that the responses obtained were so diffuse that the stimulation was valueless to the surgeon. White and Sweet[2] have also expressed this opinion.

Hyndman and Van Epps[18] have suggested that analgesia might be limited to certain dermatomes. In our opinion, this is neither wise nor practical, because of the marked intermingling of the spinothalamic fibers from different dermatomes and hence the difficulty of obtaining a localized analgesia.

Postoperative Phenomena

In the days following chordotomy, many changes in the function of the spinal cord occur as local shock, edema and hemorrhage recede and the neural pathways are reorganized.

Changes in sensory loss—The level and degree of sensory loss produced by chordotomy may change within a few days, months or years after operation. In one patient, a 50 year old woman with carcinoma of the vulva, the level dropped from T8 to T10 within four or five days after unilateral cervical chordotomy. The level may be retained for an indefinite period, as in one patient in whom it was unchanged seven and a half years after surgery.

Occurrence of pain in another location—Because of the vagaries of the primary condition, pain in some part of the body rostral or opposite to the site of the chordotomy may become troublesome shortly after the operation. The severity of the original pain may mask other painful areas.

In 11 patients, pain developed in a location other than the primary site within a few days after chordotomy. In 10 of these patients the chordotomy was unilateral. In four, chordotomy on the opposite side had to be performed subsequently, and in one patient the chordotomy was deepened on the original side. The result following the second chordotomy in these cases was not as good as the result of the primary procedure. Although 10 of the 11 pa-

tients originally had obtained relief of pain, the second operation gave complete relief in only two cases; one patient had slight improvement, and the fourth patient obtained no relief. The deepening of the original chordotomy incision did not improve the condition of the fifth patient.

One might have predicted the recurrence of pain in some of these patients by careful evaluation of their histories, for many patients will ignore a painful part when they have more severe pain elsewhere. For this reason, we wonder whether bilateral chordotomy should be performed in every case in which there is pain due to a malignant tumor somewhere near the axial portion of the body. By this means it might be possible to prevent pain which otherwise might occur with extension of the growth. That chordotomy may protect against future pain is demonstrated by the case of a 63 year old man who had a thoracic chordotomy for intractable pain in the left foot due to vascular insufficiency and who, on the second postoperative day, had a painless infarction of the left anterior tibial artery. The considerable homolateral component in the spinothalamic tract[19] may account for the fact that a unilateral chordotomy may be adequate to relieve midline pain if the patient has only a short survival period.

Secondary Chordotomy

Second chordotomy—In five patients, secondary chordotomy was performed within a few days of the primary procedure. Four of these patients obtained a satisfactory result, two having complete relief and two having partial relief of pain. One patient remained in shock following the chordotomy; oliguria developed, and the patient died nine days after the second procedure. In three patients, secondary chordotomy was performed some years after the primary procedure. Two of these three patients obtained complete relief following the second chordotomy, and the third required yet another chordotomy for relief of pain. The over-all results of secondary chordotomy (five patients with complete relief, four with partial relief, one failure, one death) are not as good as the results of primary chordotomy. The incidence of complications is also higher than after primary chordotomy.

Chordotomy following sympathectomy—Seven patients had undergone sympathectomy previously without obtaining relief of pain. All were benefited by chordotomy, five obtaining complete relief of pain. In one case, that of a 58 year old white man with an abdominal aneurysm and pain in the right foot, a unilateral thoracic chordotomy completely relieved the pain but for only one month; two years later, sympathectomy was performed, without producing relief. A year later chordotomy was repeated, again without benefit.

Chordotomy and lobotomy—Six patients have had both lobotomy and chordotomy. Four did not obtain relief of pain for more than a few weeks following chordotomy, and subsequent lobotomy produced satisfactory results in all cases. In two patients, a unilateral lobotomy had been performed without producing permanent relief of pain, and a subsequent chordotomy gave complete relief. Another patient, a 68 year old man complaining of intercostal neuralgia following thoracoplasty, had complete relief of pain following a cervical chordotomy for about a month, but then the pain recurred. A year later, lobotomy, performed elsewhere, failed to benefit the patient; electroshock therapy likewise failed to help.

Sequelae of Chordotomy

A number of neurologic abnormalities may follow chordotomy and persist for a short or a long time (table 6).

1. Incontinence of urine—Many patients had some form of urinary disturbance immediately after chordotomy, although a considerable number having unilateral chordotomy were able to void immediately after operation. The term "temporary" is used herein to denote a urinary disturbance requiring catheterization for more than three days and as long as a month. A temporary impairment of micturition might be expected in view of the probable interruption by the chordotomy incision of the centrifugal pathways for innervation of the urinary bladder.[20] Of 32 patients who had urinary disturbances following chordotomy, only 14 had incontinence which per-

TABLE 6

COMPLICATIONS FOLLOWING ANTEROLATERAL CHORDOTOMY

COMPLICATION	PATIENTS	MEN	WOMEN	CERVICAL CHORDOTOMY		THORACIC CHORDOTOMY		DEGREE OF EARLY POSTOPERATIVE RELIEF		
				Unilateral	*Bilateral*	*Unilateral*	*Bilateral*	*Complete*	*Fair*	*None*
Retention of urine	32	16	16			13	19	26	5	1
Temporary	18	8	10			10	8	14	3	1
At time of discharge	14	8	6			3	11	12	2	
Motor weakness	25	12	13			9	16	21	4	
Temporary	16	8	8			5	11	13	3	
At time of discharge	9	4	5			4	5	8	1	
Root pain at chordotomy site	12	7	5	2	1	4	5	9	3	
Temporary	9	5	4			4	5	7	2	
At time of discharge	3	2	1	2	1			2	1	
Decubitus ulcers	3	2	1		1		2	2	1	
Miscellaneous	7	3	4	3		2	2	6	1	

sisted after the time of discharge. One patient, a 45 year old white man with severe lumbar spondylosis, obtained complete relief of pain following unilateral thoracic chordotomy but had persistent difficulty in starting the urinary stream, some weakness of the ipsilateral leg, and loss of libido. It should be noted that eight of the patients who had urinary sequelae had bladder difficulty prior to the operation, so the postoperative difficulty is not necessarily attributable to the operation. Urinary disturbances were equally common in women and in men (16 cases each).

2. Weakness—Weakness of the lower extremity or extremities was the second most common complication, occurring in 25 patients. Only seven had had some impairment preoperatively. Excluding these seven patients, only two patients had weakness which persisted longer than the period of hospitalization. Within a short time these patients were able to walk, but they had slight weakness for five to six years.

It must be admitted that patients with bladder disturbance or weakness of the legs are somewhat more likely to have complete relief of pain than are those who do not have such neurologic complications. Forty-seven of the 57 patients with such disturbances (82 per cent) were completely relieved of their pain.

3. Dermatomal pain—Twelve patients had pain in the distribution of the nerve root manipulated at the time of chordotomy, and in three this pain persisted longer than the period of hospitalization. One of these patients had a posterior rhizotomy at the time of chordotomy. Of the 109 patients who did not have nerve-root pain, nine had posterior rhizotomy at the time of chordotomy. These findings would not offer much evidence to support the suggestion of Leighton,[21] who in 1921 advised section of the posterior root at the site of chordotomy to prevent postradicular pain.

4. Depression of blood pressure—Eight patients had marked hypotension. Seven of these eight patients (two of whom had unilateral chordotomy) had complete relief of pain. The patients' ages ranged from 41 to 63 years and averaged 55. White and Sweet[2] reported that in their series six patients had a fall in blood

pressure to shock levels. Disturbances in blood pressure are not uncommon after bilateral thoracic chordotomy and are even more frequent after cervical chordotomy. In Sjöqvist's[22] series a temporary drop in blood pressure occurred in 25 (17 unilateral and eight bilateral) of 58 cases. Usually, these hypotensive changes are transient and the pressure returns to normal before the patient is ambulatory. However, hypotension may persist indefinitely and be quite incapacitating.[23] Sjöqvist[22] reported the persistence of hypotension in one patient for more than two years.

In our series, only three patients had a drop in blood pressure to shock level. The first was a patient who had a two stage bilateral thoracic chordotomy for relief of pain due to carcinoma of the cervix. The second was a patient who had a bilateral chordotomy for gastric crises. This patient's blood pressure remained at hypotensive levels for five years and was so annoying that various methods had to be used to enable him to get around without fainting. It is interesting that this patient had some hypertension prior to operation (170/110 mm. Hg). This persistent hypotension in the face of previous hypertension is certainly unusual, for Hyndman and Wolkin[24] noted that in all their cases the blood pressure returned to hypertensive levels within 6 to 20 months. The third patient in whom the blood pressure fell to shock level had a bilateral chordotomy for intractable pain due to carcinoma of the lung. The blood pressure remained at shock level for eight days. Even with blood transfusions and vasopressor drugs the pressure could not be elevated, and the patient died.

Decubitus ulcers and miscellaneous complications—In three patients, bed sores developed which seemed to be related not to the chordotomy but rather to the previous debilitated state. A cerebrospinal fluid leak developed in one case; it cleared on the ninth day after surgery. A spinal fluid fistula also developed in another patient at the site of a unilateral cervical chordotomy, following a wound infection; meningitis ensued, but the patient recovered.

Sexual disturbances—It is well known that, in men, impotence may follow chordotomy. Oldberg[25] and Stookey[26] stated that although the patient may have an erection he does not ejaculate or experience an orgasm. Olivecrona[27] noted that the disturbances, particularly after unilateral chordotomy, often are temporary. In this series, four patients had disturbances in sexual activity. It should be noted, however, that many of the patients had primary conditions so debilitating that sexual activity had ceased some time prior to the time of the chordotomy. One white man, 66 years of age, was unable to obtain a penile erection following a unilateral thoracic chordotomy which relieved the pain of intercostal neuralgia. A 35 year old woman who obtained complete relief of pain after a bilateral thoracic chordotomy for gastric crises experienced a diminution in sexual pleasure after the operation, but normal sensation returned within 19 months and has not diminished during a seven and a half year follow-up. A 55 year old man who underwent bilateral thoracic chordotomy for gastric crises had temporary loss of libido and orgasm for about a year, but at a follow-up interview more than five years after the operation the patient stated that he had no sexual disturbances. In both the latter patients, sexual function probably was impaired by the primary disease, for tabetic persons commonly are impotent. A 45 year old white man was relieved of the pain of severe lumbar spondylosis by a bilateral thoracic chordotomy but had marked impotence which has persisted for six and a half years (the duration of follow-up). Reduction or loss of sexual pleasure is less frequent in women than in men. A number of factors might contribute to this difference, and so the fact that only one woman in this series and one in White and Sweet's[2] series complained of the absence of erotic sensation despite unimpaired libido may not be considered too significant.

Paresthesias—Only one patient complained of paresthesias. She was a 31 year old woman who had a bilateral cervical chordotomy for relief of pain due to carcinoma of the cervix. The pain was relieved completely, but she had paresthesias in the hypalgesic hand.

Mortality—Based on the criterion that any patient who dies before leaving the hospital

should be included in the operative death rate, the mortality in this series is 5 per cent. White and Sweet[2] reported a mortality rate of 4 per cent. There is no doubt that the primary condition is an important factor in the mortality rate, for most of the patients dying after chordotomy had malignant disease. Four patients with malignant disease died, and two with nonmalignant disease. A 47 year old man who had phantom pain in the left leg died of a pulmonary embolism 17 days following a unilateral thoracic chordotomy, and a 54 year old man with a painful phantom right arm died of pneumonia two weeks after unilateral cervical chordotomy.

Long-Term Results of Chordotomy

Because follow-up observations have been made only of the patients who underwent operation at The Johns Hopkins Hospital, the discussion of the late results of chordotomy is based on the 79 patients in that group. Three patients died before leaving the hospital, and the fate of 45 of the remaining 76 patients has been ascertained by letter or personal interview. The other 31 could not be located or did not respond to letters of inquiry. That these 31 patients represent the same population as those contacted is impossible to say. Probably the majority having malignant disease are dead; their fate is unknown.

Of the 45 patients whose status is known, five died within two months of operation, 10 more died within six months, eight more died within one year, four more died in the second year, and four more died thereafter, for a total of 31 deaths.

Of the group with malignant disease, 21 patients who survived the initial postoperative period lived an average of seven and a half months; more than one-third, 9 of 21, did not survive longer than three months after operation. Most of the patients with malignant disease had complete relief of pain for their short period of survival of two to three months. Three patients required a subsequent lobotomy which relieved the pain completely. A 37 year old woman with carcinoma of the cervix had complete relief of pain for seven years after unilateral thoracic chordotomy; then, because of recurrence of pain on the opposite side, a second chordotomy was performed which again relieved the pain completely. Even those patients in whom the original pain returned or new pain developed usually could be made comfortable with medication.

In assessing the results of operation, some idea of the benefit may be obtained by noting the medication required. A 56 year old Negro man with sarcoma stated that although he had only 50 per cent relief of pain he no longer needed medication. Another patient stated that for a month or so following operation he suffered as much pain as before operation, or more, but he did not require medication such as he had demanded previously.

The patients with non-neoplastic diseases have been followed for a relatively long period. Two patients with gastric crises have had complete relief from these attacks, one (a 35 year old white woman) for seven and a half years and the other (a 55 year old man) for five and a half years. A 45 year old man who had a unilateral thoracic chordotomy for lumbar spondylosis has been completely relieved of his pain for six and a half years; however, he still has some difficulty controlling his urinary bladder, some weakness of the legs, and impairment of libido. A patient with tabes dorsalis and hot, shooting precordial pain radiating to the axilla has had complete relief for a period of five years following a unilateral cervical chordotomy.

Fourteen patients are known to be alive two months to 10 years after chordotomy. We may assume that after two years the status of the patient has reached a plateau and will change little. Hence, a fair evaluation of the effects of chordotomy would seem to be an assessment of the patient's condition until death or during the two years following chordotomy. On this basis we can evaluate the results in 36 patients. Twenty-one (58 per cent) had complete relief of pain until death or two years after the operation, seven (20 per cent) had fair relief so that the discomfort was bearable, and eight (22 per cent) have not had significant improvement. Of nine patients who were operated on less than two years ago, three report complete relief of pain, two fair relief, and

four no relief. Of the patients in whom the results of chordotomy after two years are known, 78 per cent had satisfactory relief of pain.

Summary

An analysis of a series of 121 patients in whom chordotomy was performed reveals that 67 per cent obtained complete relief of pain, 21 per cent had a fair result, 7 per cent failed to obtain relief of pain, and 5 per cent have died or have been lost to follow-up. Women obtained slightly better results than men. The results were the same in patients with neoplastic diseases and in patients with non-neoplastic diseases (67 per cent complete relief).

Early postoperative results were not appreciably influenced by the presence of acute or chronic pain or by the presence or absence of addiction. Relief of pain did not parallel the degree or extent of sensory loss. There were patients with incomplete analgesia and complete relief of pain and others with pain in the analgesic area.

It is believed that better results may be obtained if local anesthesia is used. The decision as to the type of anesthesia will depend on the patient, on the practice of the surgeon, and on the anesthesiologist.

Incontinence of urine (32 patients), weakness of an extremity (25 patients), root pain at the operative site (12 patients), and depression of blood pressure (eight patients) were the most frequent complications.

The mortality rate was 5 per cent. The average survival time in the neoplastic group was seven and a half months.

Of the patients whose fate is known for at least two years after chordotomy, 58 per cent had complete relief of pain until death or for two years, 20 per cent had fair relief, and 22 per cent did not obtain relief of pain.

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The Diagnosis of Curable Unilateral Renal Hypertension by Ureteral Catheterization

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A new concept in the diagnosis of curable renovascular hypertension is presented, based on comparative measurement of reabsorption of water in the two kidneys.

The requisite conditions for measuring maximal reabsorption of water in the presence of renal ischemia and the technic for obtaining meaningful data by ureteral catheterization are presented in detail.

With the method described, diagnosis as well as treatment of curable renovascular hypertension is specific.

Aortography, with its attendant artefacts, risks and equivocation concerning the functional significance of an anatomic lesion, is rarely necessary in the treatment of these patients.

THOMAS A. STAMEY

GOLDBLATT presented his classical treatise on the production of hypertension in the dog by constriction of the renal arteries in 1934, but as late as 1953 few investigators believed that these experiments were applicable to human hypertension. The major argument against the occurrence of the Goldblatt phenomenon in man was the scarcity of acceptable cases; even in 1952, reviews on this problem listed as acceptable only one or two reported cases, and these with considerable reservation. In 1953, Howard, Berthrong, Sloan and Yendt[1] succinctly documented the clinical course of four patients with malignant hypertension who were cured by nephrectomy. All four patients had gross obstruction in the main renal artery of the diseased kidney. The enlivened interest in this subject during the past few years dates from this report by Howard and associates, and in the current enthusiasm over the best method to diagnose curable renovascular hy-

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pertension the debt owed to these authors is sometimes forgotten.

It is the purpose of this paper to present a new concept in the functional diagnosis of renovascular hypertension based on a remarkable reabsorption of water in the ischemic kidney. The conditions as well as the exact technic for measuring this reabsorption of water will be presented in detail.

The Functional Characteristic of Renovascular Hypertension

Research over the past three years, the details of which will be published elsewhere, has established the following points in regard to unilateral renal disease.

1. The basic characteristic of unilateral renal ischemia associated with curable hypertension is an excessive reabsorption of water as the glomerular filtrate passes down the ischemic nephron.

2. All other types of unilateral renal disease, occurring in normotensive patients, fail to show this increased reabsorption of water. For example, calculous disease, renal tumor, pyelonephritis and simple congenital disparity in size of the kidneys all are strikingly different in their comparative patterns of reabsorption of water. In fact, unilateral renal disease in normotensive patients is characterized by a pattern exactly opposite to that of renal ischemia; in the former there is a *failure* to reabsorb water because of medullary damage to the concentrating mechanism. If there is a disparity in size of the kidneys due to an original difference in the renal mass present at birth, the comparative patterns of reabsorption of water are the same. Unilateral renal ischemia, therefore, is different in its functional pattern from all other forms of renal disease and can be recognized by comparative measurement of the reabsorption of water in the ischemic kidney and in the nonischemic kidney.

Use of PAH in Measuring Comparative Reabsorption of Water

Figure 1 illustrates the functional lesion characteristic of renal ischemia and the method of measuring this phenomenal movement of water. In this technic of studying the comparative reabsorption of water, inulin is classically used because it crosses the glomeruli of both the normal and the "diseased" kidney in equal concentrations. Since inulin is not reabsorbed in passing down the nephron, the comparative concentrations of the two kidneys serve as an index of the relative difference in reabsorption of water. Whereas inulin has been used in all these studies, it is now clear that para-aminohippuric acid (PAH) is equally indicative of comparative reabsorption of water. Because determination of the concentration of PAH is a simple laboratory procedure,[2] well within the range of routine hospital determinations, the use of PAH rather than inulin is recommended.

PAH is secreted by the proximal tubule into the tubular urine. Reduced renal blood flow, which is *always* present in renal ischemia, means that less PAH is secreted per minute into the proximal tubular urine. Our studies of curable unilateral renal hypertension show clearly that the reduced quantity of PAH per minute is secreted into an almost equally reduced volume of glomerular filtrate. In other words, the filtration fractions for the two kidneys are rarely different. Even when there is some disparity, the degree of excessive reabsorption of water in the ischemic kidney is so great that the difference in filtration fractions becomes insignificant. Therefore, from the practical standpoint (although not from the theoretical) PAH is as satisfactory as inulin in the measurement of this comparative reabsorption of water.

Let us consider the diagram in figure 1 further. In saying that the filtration fractions are approximately equal, and that in any case the difference between them is insignificant compared with the dramatic changes along the nephron, we are really saying that PAH begins its course down the nephrons of both kidneys in nearly equal concentrations. Suppose, as in the diagram, that renal blood flow has been reduced by 40 per cent in the ischemic kidney. With the same reduction in glomerular filtration (equal filtration fractions), one would expect a 40 per cent reduction in urinary volume, or a volume of 60 ml.

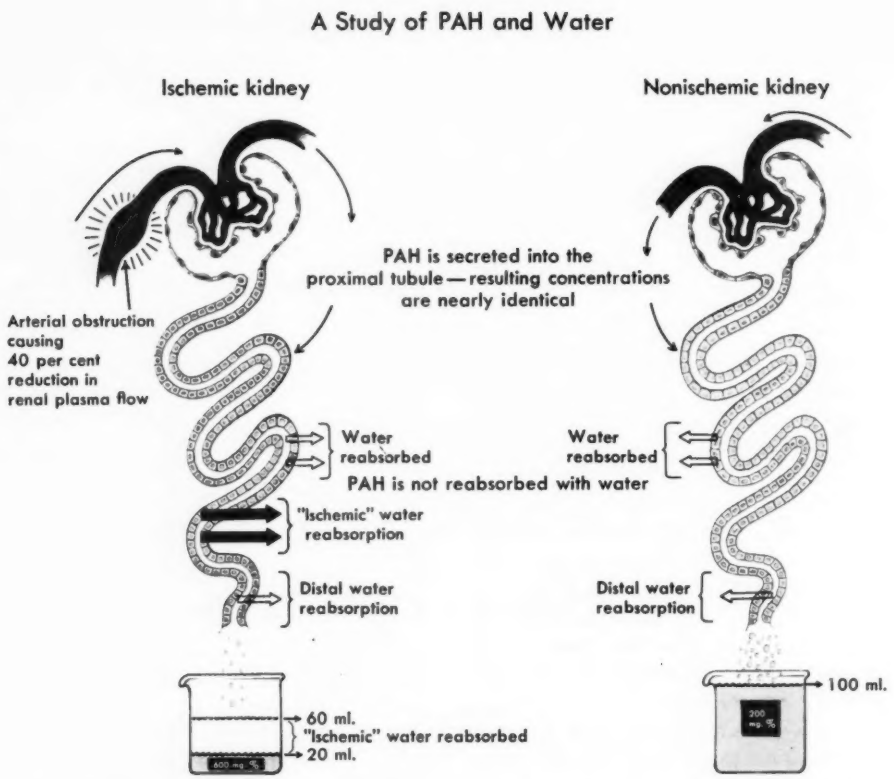
A Study of PAH and Water
Ischemic kidney
Nonischemic kidney
PAH is secreted into the proximal tubule — resulting concentrations are nearly identical
Arterial obstruction causing 40 per cent reduction in renal plasma flow
Water reabsorbed
Water reabsorbed
PAH is not reabsorbed with water
"Ischemic" water reabsorption
Distal water reabsorption
Distal water reabsorption
100 ml.
60 ml.
"Ischemic" water reabsorbed
20 ml.

FIGURE 1. Diagram illustrating the functional lesion characteristic of renal ischemia and the method of comparative measurement of reabsorption of water in the two kidneys for the diagnosis of curable unilateral renovascular hypertension.

compared with the 100 ml. excreted from the nonischemic kidney. Since PAH is not reabsorbed with water, this 60 ml. would have the same concentration of PAH (200 mg. per cent) as the urine from the normal kidney. This does not happen. What actually occurs is a phenomenal increase in reabsorption of water, so much so, in fact, that 20 ml. of water is obtained, not 60 ml. The PAH will be concentrated to 600 mg. per cent by this extra reabsorption of 40 ml. of water out of the nephron. It is this concentration of PAH, 600 mg. per cent compared with the 200 mg. per cent in the kidney excreting the larger quantity of water, that tells the investigator that marked reabsorption of water has occurred in the kidney excreting the smaller quantity of water. In other words, in the diagram, 300 per cent more water has been reabsorbed in the ischemic kidney than has been reabsorbed in the normal kidney.

Suppose a patient simply had a congenital disparity in the size of the kidneys, one being 40 per cent smaller than the other. The renal blood flow (the *clearance* of PAH) would also be reduced by 40 per cent in that kidney. It would then excrete 60 ml. of urine compared with an excretion of 100 ml. from the opposite kidney, and the concentration of PAH would be the same in the urine from either kidney.

If the 40 per cent reduction in renal blood flow resulted from pyelonephritis or calculous disease causing a 40 per cent destruction of renal tissue, then the affected kidney would excrete, in a normotensive patient without

ischemia, *more than* 60 ml. of urine, because the medulla would not reabsorb the same proportion of urine as the medulla in the contralateral normal kidney. Therefore, the concentration of PAH would be less in the urine from the pyelonephritic kidney and exactly proportional to the amount of urine excreted in excess of 60 ml.

It is worth emphasizing that only in renal ischemia is less urine excreted than the amount predicted by the ratio of glomerular filtration rates or, for practical purposes, that predicted by the ratio of renal plasma flows (Cl_{PAH}). If this measurement is used, curable hypertension caused by ischemia of as little as one-third of one kidney (segmental ischemia) is readily recognized by ureteral catheterization. These lesions previously escaped functional detection by ureteral catheterization. Although the involved kidney excreted less urine, the sodium concentration was equal to that of the normal kidney or even greater. When aortography has been employed, segmental ischemia has been missed many times because of failure to visualize and interpret correctly the more distal, smaller arteries. In the patients studied by the technic of measurement of the comparative reabsorption of water, segmental renal hypertension has been associated with a reduction of at least 40 per cent in the urinary flow rate and an increase of 20 to 60 per cent in urinary concentration of PAH compared with the contralateral kidney. On the other hand, obstruction of the main renal artery has been associated with an increase of 100 to 600 per cent in the urinary concentration of PAH from the ischemic kidney, the percentage depending on the degree of reduction in renal blood flow, and with a reduction of at least 50 per cent in urinary flow rate. These observations, as well as the 20 to 60 per cent increase in concentration of PAH in the urine from segmentally ischemic kidneys, contrast sharply with the findings in unilateral renal disease in normotensive patients, in which any degree of reduction in urinary flow rate may occur, depending on the degree of renal damage, and the concentration of PAH is never increased by more than 5 per cent (the maximal error of the method when the concentrations are actually equal).

Because of this striking difference between control subjects and patients with curable unilateral renal hypertension, aortography has been abandoned—without regret. Not only does aortography constitute a certain incalculable risk to the patient, but many times unsatisfactory aortograms are obtained. Even when they are satisfactory, the actual demonstration of an anatomic lesion does not prove that a reduction in blood flow is present. A very sizable arterial obstruction to the kidney must occur before a functional defect in renal blood flow (ischemia) is measurable, and therefore before hypertension is produced. An anatomic defect can be present without being functionally significant in relation to the patient's hypertension.

Aortography is equally unnecessary in planning therapy. As already indicated, in order for an obstruction in a main renal artery to cause a functional reduction in blood flow to a kidney, there must be a significant drop in arterial pressure (at least 50 mm. Hg, and usually much more) across the obstruction. Thus, an obstruction of the main renal artery either will be plainly visible to the vascular surgeon or will be easily measurable by strain-gauge manometry if any question arises. If there is no significant drop in blood pressure between the aorta and the most distal point of the main renal artery in the hilus of the kidney, the surgeon is dealing with distal segmental ischemia. In the latter case, if inspection of the surface of the kidney and the first branches of the main renal artery reveals a resectable segmental lesion, partial nephrectomy may be performed. If these changes are not observed on the surface of the kidney but the surgeon has definite knowledge that the functional lesion described is present, nephrectomy may be performed confidently.

Conditions Necessary for Meaningful Ureteral Catheterization

As already stated, the research which has established the evidence on which this report is based will be presented in detail elsewhere.

1. Bladder leakage must be prevented. This is easily accomplished by using whistle-tip

polyethylene catheters* and following carefully the instructions given in the section titled "Technic."

2. Urinary flow rates must be at least 2 ml. per minute per kidney or more. If the flow rate is less than this amount, it does not represent the true urinary output for that kidney, and consecutive 10 minute collection periods are not repeatable in terms of ratios of urinary excretion; this is primarily because of dead-space errors. At very slow rates of flow, reabsorption across the pelvic and ureteral mucosae plays a significant role.

The only exception to this requirement is a reduction in renal blood flow so great that the ischemic kidney cannot possibly excrete urine at a rate of 2 ml. per minute. Under these circumstances, however, the contralateral normal kidney usually will have a flow rate of 10 to 20 ml. per minute and there will be little doubt as to the existing condition.

3. The ureteral catheters should be introduced only to a point approximately in the middle of the ureter. After both catheters have been inserted, the 10 minute collection periods must not begin for at least 10 minutes, and a delay of 15 minutes is preferable. The catheter, as a foreign body, sets up sympathetic ureterorenal vasoconstrictive reflexes which produce an artificial fall in renal plasma flow and urinary flow rates. It is to avoid the risk of increased trauma and the production of even more severe reflexes that the catheters purposely are not inserted all the way to the renal pelvis. Within 15 minutes the reflexes from catheterization have "settled down" and the comparative study may proceed. If, for any reason, the ureteral catheters are adjusted during the study, another 15 minutes must elapse before collections are resumed.

4. As a definitive measure of renal function, *three consecutive 10 minute collection periods* are required. The ratios of the urinary flow rate (the flow rate of the ischemic kidney over the flow rate of the normal kidney) in these periods *must agree within 2 to 8 per cent*. Under these conditions there can be little doubt that true, comparable renal function has been measured.

5. Urea must be infused, for several reasons, the most important one being that urea increases the *relative* reabsorption of water in the ischemic kidney. The ischemic kidney, because of reduced glomerular filtration, has less urea presented to the medulla than has the contralateral kidney. The medullary gradients of urea, necessary for maximal urine concentration, are therefore lacking in the ischemic kidney. Another reason for the infusion of urea is that urea maintains the necessary urinary flow rates for repeatable data. Without an osmotic diuretic (and urea is the only acceptable agent) meaningful catheterization data are practically impossible to obtain. Finally, when the catheters are removed, urinary flow rates are increasing rather than decreasing, and urea thus reduces to a minimum the postcatheterization problems of ureteral colic from blood clots.

6. Antidiuretic hormone (ADH*) also must be infused. Five milliunits of ADH per kilogram of body weight per hour does not produce side effects and assures the presence of 5 to 10 times the minimal amount necessary for maximal reabsorption of water in the normal kidney. The distal tubules of both kidneys are thus reabsorbing water under a maximal stimulus insofar as ADH is concerned.

7. The urea and ADH should be given in saline to replace the salt loss resulting from the osmotic diuresis.

Technic

The major purpose of this paper is to present in detail, with exemplary calculations, the exact technic for measuring the characteristic reabsorption of water in curable renovascular hypertension. It is believed that this procedure is well within the range of practice of the interested practitioner and urologist.

The physician should explain the procedure to the patient several days before the study is to be made, so that he will understand that the test does not produce pain and particularly

*We have used the standard polyethylene catheters manufactured by the American Cystoscope Makers, Inc. They are inexpensive compared with the usual woven catheters.

*PITRESSIN® (Parke, Davis & Company).

that the cystoscope will be introduced under complete regional anesthesia.

If the patient is taking a saluretic drug, its use should be discontinued several days before the test. However, this precaution is unnecessary if there is good reason to continue the medication.

On the day cystoscopic examination is to be performed, the patient is allowed a liquid breakfast of his own choice and is encouraged to force fluids for the two hours preceding the test. The exact quantity of fluid is unimportant, because the urea will maintain an excellent urinary output.

The patient arrives at the room where cystoscopy is to be performed and takes a sitting position on the edge of the table. His blood pressure is recorded. An 18 gauge needle with a three-way stopcock is used to withdraw approximately 15 ml. of blood, which is placed in a chemically clean test tube.

The loading dose of PAH is then injected. This is readily calculated beforehand by multiplying the weight of the patient (in kilograms) by 0.035.* The resulting figure represents the number of milliliters of 20 per cent PAH to be injected. For example, a 70 kg. man would receive 70 x 0.035 or 2.45 ml. of 20 per cent PAH. PAH is supplied in 10 ml. ampules by Merck Sharp & Dohme.

After the loading dose of PAH has been injected, the urea-saline-ADH infusion is started at a rate of 10 ml. per minute. The time is recorded. This infusate may, at first glance, seem complicated, but the preparation is simple and actually can be reduced to "cookbook" directions. From a 1000 ml. bottle of intravenous saline (which contains about 1,050 ml.), withdraw 160 ml. of saline. Use 100 ml. of this by injecting 50 ml. into each of two 40 gm. bottles of Abbott's UREAPHIL® (U.S.P. crystalline urea); shake bottles well until the solution is completely mixed (this may require 5 to 10 minutes). Then withdraw the contents of each urea bottle (now about 80 ml. in volume) and replace in the intravenous saline solution. The resulting solution should be completely clear. There is now 80 gm. of urea in 1,050 ml. of saline (approximately an 8 per cent solution).

The amount of PAH to add to the infusate is always constant; however, it does depend on one of three estimates of the patient's renal function:*

1. If the blood urea nitrogen (BUN) or serum creatinine value is within normal limits, and if the 15 minute phenolsulfonphthalein (P.S.P.) excretion is 30 per cent or more, add 7.9 ml. of PAH to the saline-urea bottle.

2. If the BUN or serum creatinine value is within normal limits but the 15 minute P.S.P. excretion is less than 30 per cent, some renal damage is present. In this case, add 5.3 ml. of PAH to the saline-urea bottle.

3. If the patient is uremic, marked renal impairment is present. Add only 2.6 ml. of 20 per cent PAH to the saline-urea bottle.

The amount of ADH (Pitressin) to be added to the saline is 1.8 times the loading dose. The loading dose of ADH is 5 milliunits per kilogram of body weight. Rather than calculate the amount on the basis that 1 ml. of Pitressin is equivalent to 20,000 milliunits, one may use a more direct method. Take 1 ml. of Pitressin and add 19 ml. of saline (we usually use some of the remaining 160 ml. originally removed from the saline bottle). This gives a 1:20 dilution. The loading dose of ADH will always be a fraction of 1 ml. of this 1:20 dilution equal numerically to one-half the weight of the patient in kilograms. Note carefully that an 80 kg. man would receive only 0.4 ml. of the 1:20 dilution as a loading dose. The amount of ADH to add to the infusate is calculated as follows: $1.8 \times 0.4 = 0.72$ ml. of the 1:20 dilution. This should be measured with a tuberculin syringe, injected into the saline bottle, and the loading dose of the 1:20 dilution should be drawn up into the same syringe and saved for later injection. The 1,050 ml. of intravenous saline now con-

*The number 0.035 is based on a PAH space estimated at 28 per cent of body weight, to give a concentration of PAH in that space of 2.5 mg. per 100 ml., using a 20 per cent solution of PAH for injection.

*These calculations of the amount of PAH are based on estimates of renal plasma flow of 600, 400 and 200 ml. per minute, respectively, to maintain a plasma level of 2.5 mg. per 100 ml. of PAH, at a rate of infusion of 10 ml. per minute from a total infusate of 1,050 ml.

tains PAH, 80 gm. of urea, and 1.8 times the loading dose of Pitressin (5 milliunits per kilogram).

The entire procedure, up to this point, aside from the preparation of solutions, has consisted of drawing a blood sample, injecting the loading dose of PAH, starting the intravenous saline mixture at a rate of 10 ml. per minute, and giving the loading dose of ADH intravenously 5 or 10 minutes later. At the most, 15 minutes have elapsed. The physician should be aware of the rate of delivery of the infusion set, especially how many drops are equal to 1 ml.

A "saddle" zone of deep anesthesia is now produced with NUPERCAINE® (Ciba Pharmaceutical Products), which is rapid and highly effective. This requires a lumbar puncture in the sitting position, a single injection of 0.6 to 1.0 ml. of a 0.25 per cent solution from a 2 ml. ampule being given. There is no mixing of solutions, and little time is wasted. A lower lumbar interspace is used for the injection. The patient remains in the sitting position for another 15 minutes, and a perfect saddle anesthesia results which involves only the perineum and does not affect renal blood flow. The patient may drink more water during this period. Fifteen minutes after the anesthetic is given, he is placed in the lithotomy position and the genitalia are prepared for cystoscopy.

A No. 24 Brown Buerger cystoscope is introduced into the bladder, and a culture of the urine is obtained. After inspection of the bladder, the double catheterizing element* containing a pair of No. 8 French polyethylene whistle-tip catheters is introduced. The important point in preventing bladder leakage, in addition to the use of these wide-bore polyethylene catheters, is the *relation of the size of the ureter to the size of the catheter*. The cystoscopist should begin with a No. 8 French, since about 60 per cent of all ureteral orifices will readily accept a catheter this size. If a No. 8 French catheter will not negotiate the ureteral orifice, it is removed and a No. 7 French catheter is tried. If this fails, a No. 6 is introduced. Very rarely will a smaller catheter be required. These catheters should be introduced only to approximately the middle of the ureter; the exact point is not critical. After both ureters have been catheterized, the time should be recorded and a specific notation made regarding any difficulty in catheterizing either ureter.

Approximately 45 minutes have now elapsed, and 450 ml. of the infusion has been absorbed. Fifteen minutes more are needed for the sympathetic reflexes to subside. This period can be utilized to advantage. A strip of adhesive tape is placed from knee to knee, passing under and supporting the cystoscope. The instrument is disconnected from all tubing, and both cystoscopic stopcocks are opened to facilitate emptying the bladder. Suprapubic pressure often is necessary to obtain more rapid emptying. Once the bladder is completely empty, the water tubing is reconnected to the cystoscope, closing the opposite stopcock. A few milliliters of the irrigating water (10 to 30 ml.) are run into the bladder, the water tubing again is disconnected, and the stopcocks are opened. There should be an immediate rush of the irrigating water out of the open stopcock. This is important, because it assures the cystoscopist that if leakage occurs around the ureteral catheters into the bladder it will be immediately apparent at the open stopcock.* This point serves to emphasize the remarkable control and confidence the cystoscope gives the investigator in his concern over bladder leakage. It is apparent that if there is no leakage at the open stopcock it is not even necessary to disturb the patient between collection periods by exerting suprapubic pressure on the bladder.

The waiting period of 15 minutes after in-

*The double catheterizing element must not contain a center fin, because if it does, the instrument will not accept two No. 8 French polyethylene catheters.

*The dynamics of bladder drainage in this technic have come as a surprise. It is almost as if a positive pressure exists around the bladder end of the cystoscope. For example, in studies where one ureteral catheter was removed after many periods in the absence of bladder leakage, we were surprised to find that urine appeared at the open stopcock in the same peristaltic fashion as when the ureteral catheter was in the ureter. Further, suprapubic pressure fails to produce further drainage at the open stopcock.

troduction of the ureteral catheters can be utilized not only in assessing these aspects of bladder leakage and dynamics but also in obtaining cultures of urine samples from both kidneys. The cultures must be placed in a nutrient broth, for example, thioglycollate, because the rapid diuresis can reduce bacterial colony counts to quite low numbers. The assumption that 100,000 bacteria or more represent a significant infection has no place in direct renal cultures.

About one hour after administration of the loading dose and initiation of the infusion (the time required for equilibration with body fluids), consecutive 10 minute collections may begin. These must, of course, be timed to the exact second. Collections are easier if a stand is provided which is designed to hold 50 ml. graduated centrifuge tubes; this allows direct reading of the urine volumes and the flow rates during the procedure.

Although the physician needs to know only the simultaneous urinary flow rate and PAH concentration of each kidney to diagnose curable unilateral renal hypertension, a real opportunity passes if the concentration of PAH in the serum is not determined. This can be accomplished by taking a second sample of blood about midway in the 30 minute collection period (three 10 minute periods) or, more accurately, by taking a sample at the start of the collection period and after the third collection has been made. Because some PAH color occurs in normal serum, the original blood sample is drawn before the loading dose of PAH is injected. By subtracting this PAH color in the "blank" from the color in the sample taken at the midpoint of the collection period, a value is obtained which represents the true serum concentration of PAH. With this value, one can easily calculate the absolute renal plasma flow for each kidney in milliliters per minute, by the classic clearance formula:

$$\frac{U \text{ (PAH concentration in urine, milligrams per cent)} \times V \text{ (urinary flow rate, milliliters per minute)}}{P \text{ (PAH concentration in serum, milligrams per cent)}}$$

This is extremely useful information, obtainable for the price of two additional chemical determinations when six already are being made. It should be emphasized that it is not the clearance of PAH (renal plasma flow) that makes the diagnosis, but rather the comparative rates of urinary flow and the concentration of PAH. It is, in fact, quite possible for the flow rate (V) to be reduced by 50 per cent, the concentration of PAH to be increased by nearly 100 per cent (curable renal ischemia), but the renal plasma flow $\frac{U \times V}{P}$ to be reduced only a few percentage points. On the other hand, the calculated renal plasma flow may be appreciably reduced in one kidney, but there is *no renal ischemia* unless the excessive water reabsorption described herein is present.

The exact renal plasma flow is valuable additional information. For one thing, the physician can learn the extent of hypertrophy in the contralateral normal kidney, and, more importantly, he can learn whether or not the opposite kidney has a satisfactory renal plasma flow. Theoretically, this information supplies evidence concerning the all-important point of the relation of renal plasma flow to urine flow. Our data already have shown that a very small reduction in functional blood flow can cause curable renovascular hypertension which is recognizable by the marked effect on water reabsorption. Since essential hypertension may have as its only renal defect a slight reduction in renal blood flow, this reopens the entire question of essential hypertension and the kidney. Therefore, the determination of serum PAH concentration and calculation of renal plasma flow should be specifically recorded.

Complications and Morbidity

Some patients complain of headache near the end of the infusion period. DEMEROL® is an excellent medication and may be given during the procedure without fear of affecting the comparative renal measurements. In a few patients, there is a slight increase (10 mm. Hg) in the systolic and diastolic blood pressure near the end of the infusion period. This undoubtedly is due to an increase of extracellular fluid volume. For this reason, some

precaution is necessary in studying patients who have had a recent coronary occlusion or angina pectoris; 4 per cent urea should be given, and less infusate administered. One thousand milliliters of an 8 per cent solution of urea has been given at a rate of 10 ml. per minute to patients with all degrees of renal damage, even to those with a total glomerular filtration rate as low as 12 ml. per minute, and there have been no complications. The urea nitrogen concentration in the serum will be elevated for a few days after the procedure, depending on the level of renal function. One patient in 10 will have a postspinal headache lasting about 48 hours. Because the cystoscopic examination is always discontinued at a point of rising diuresis, the average patient will have a urinary output approaching 1000 ml. in the two hours following cystoscopy. Ureteral colic from blood clots almost never occurs. A few patients, especially men, in whom the Nupercaine saddle anesthesia is prolonged on the bladder may require catheterization to relieve retention. It is wise to prescribe a sulfonamide preparation for three or four days on a prophylactic basis. Remember that a very small adult or a child is better studied by administering a 4 per cent solution of urea, or an 8 per cent solution given at a rate of 5 ml. per minute; in the latter instance, the amount of PAH in the infusate must be doubled.

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The Clinical Value of Esophageal Motor Studies

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Significant strides have been made in recent years in the understanding of normal esophageal motor function. With these advances, a number of patterns have been recognized which characterize the motor disturbances of various esophageal diseases. The clinician will find this new diagnostic technic of ever-increasing value in the complete evaluation of the patient when esophageal disease is suspected.

In recent years, rapid advances have been made in the technics of measuring esophageal motility. Two principal developments have resulted: (1) The understanding of normal esophageal motor function has been enhanced significantly; (2) the elucidation of patterns of motor abnormalities, along with their clinical correlation, has evolved rapidly.[1] The accumulated experience with and the availability of these technics render them increasingly useful to the clinician in the evaluation of esophageal disease and symptomatology.

Technic of Esophageal Motor Study

In our laboratory the standard equipment consists of a train of three plastic open-tipped water-filled catheters with the tips positioned 5 cm. apart. The catheters are connected to external transducers, and simultaneous multichannel recording is performed with the patient supine. During stepwise withdrawal of the catheter tips from stomach to pharynx, resting pressures as well as deglutition pressures are measured at each level.

Normal Esophageal Motor Pattern

The esophagus is a muscular tube with a sphincter at each end. The upper sphincter, made up largely of the cricopharyngeus, maintains a resting intraluminal pressure of 10 to 45 mm. Hg above atmospheric pressure. Figure 1 demonstrates the pressure relationship in the area of the upper esophageal sphincter. During swallowing, the upper esophageal sphincter relaxes prior to the arrival of the pharyngeal peristaltic wave. Delayed or incomplete opening of the upper esophageal

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sphincter may be the basis of certain types of dysphagia localized to the hypopharyngeal region, such as dysphagia in the Plummer-Vinson syndrome, or dysphagia occurring in various neuromuscular disturbances.

Normally, peristalsis in the body of the esophagus progresses caudad at a rate of 2 to 4 cm. per second (figure 2).

At the lower end of the esophagus is a high-pressure zone which has the characteristics of an intrinsic sphincter. This high-pressure area extends for 2 to 3 cm., and maximal pressure generally is found within 0.5 cm. of the diaphragmatic hiatus (figure 3). The resting pressure of the lower esophageal sphincter exceeds intragastric pressure by 6 to 9 mm. Hg at end expiration. This sphincter apparently is the most important barrier to gastroesophageal reflux. Within 1.5 to 2.5 seconds following a swallow, and before arrival of the peristaltic wave, the lower esophageal sphincter relaxes and remains open for 5 to 12 seconds (see figure 3). The radiologic appearance of this sphincter at rest and following a swallow is seen in figure 4.

Clinical Abnormalities of Esophageal Motor Function

1. Achalasia—The clinical features of achalasia result from two abnormalities. First, swallowing is not followed by peristalsis in the body of the esophagus. This disturbance is felt to be due to the loss of ganglion cells from the myenteric plexus in the body of the esophagus. Second, the lower esophageal sphincter does not relax following a swallow. The underlying defect causing this abnormality is not known. The administration of MECHOLYL® to these patients causes tetanic contractions involving the body of the esophagus.[2] This exaggerated response to parasympathomimetic agents has been interpreted on the basis of Cannon's law and is pharmacologic evidence for absent or impaired postganglionic cholinergic innervation of the esophagus in achalasia. The response to Mecholyl may be detected radiologically or manometrically.

Case 1—A 43 year old housewife was admitted to The Johns Hopkins Hospital complaining chiefly of weight loss, abdominal pain, and dysphagia of five months' duration. Significant aspects of her past history included hysterectomy and postoperative radiation in 1958 for a grade 1 adenocarcinoma. In June 1960 she was seen in the outpatient clinic because of generalized abdominal and back pain, dysphagia and weight loss. A barium-enema study demonstrated irritability of the ascending colon. An upper gastrointestinal x-ray series demonstrated "holdup" of barium at the esophagogastric junction and suggested the diagnosis of achalasia (figure 5). Esophageal motor studies revealed progressive peristaltic motor activity throughout the body of the esophagus and normal relaxation of the lower esophageal sphincter, thus effectively ruling out the diagnosis of achalasia. The patient continued to do poorly, and in August 1960 she became icteric. Exploratory laparotomy revealed extensive metastatic carcinoma presumably arising in the head of the pancreas, with mechanical obstruction of the distal esophagus. In this case, motor studies ruled out intrinsic motor abnormality of the esophagus and implicated a mechanical obstruction at the distal esophagus.

2. Esophagitis—It is generally held that peptic esophagitis is caused by increased reflux of gastric juice. Recently, attention has been focused on the role of the lower esophageal sphincter in preventing reflux. Indeed, it has been reported that symptoms of esophagitis do not occur in hiatus hernia if a competent sphincter is present.[3] In patients with symptoms of esophagitis we have found the high-pressure area in the region of the lower esophageal sphincter to be absent or greatly diminished (figure 6).

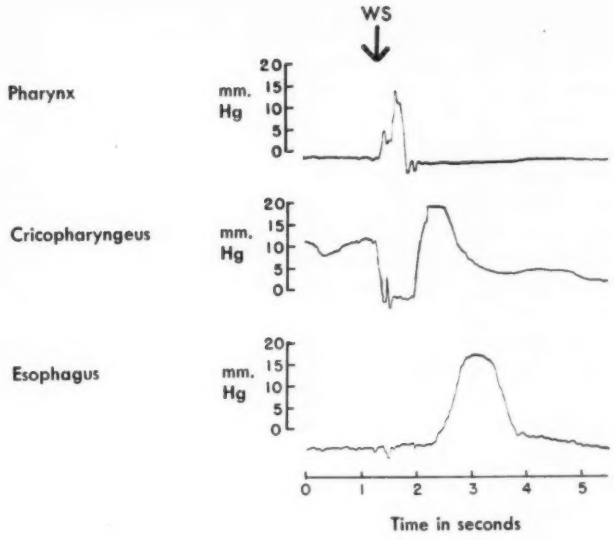

FIGURE 1. Deglutition pressures in the region of the pharyngoesophageal junction. Normal tracing obtained with the recording catheter tips in the pharynx, cricopharyngeus (upper esophageal sphincter) and esophagus. The cricopharyngeus maintains a resting pressure of 10 to 45 mm. Hg above atmospheric pressure.

With deglutition (WS, water swallow), pressure in the cricopharyngeus falls to the level of pressure in the cervical esophagus. The cricopharyngeus normally relaxes prior to the arrival of the pharyngeal peristaltic contraction. Following relaxation of the cricopharyngeus, peristalsis is observed in the body of the esophagus.

Occasionally it is impossible clinically to distinguish between the pain of coronary arterial disease and pain of esophageal disease. Esophagoscopy may not be particularly helpful because many patients whose symptoms suggest esophagitis have neither gross nor histologic evidence of esophageal inflammation. The use of acid perfusion of the esophagus as a diagnostic test is of value in these patients.[4] The test is positive when acid perfusion duplicates the spontaneously occurring pain and produces concomitant motor abnormalities, which consist of an increase in spontaneous (often synchronous) motor activity and, frequently, a change in the configuration of the primary peristaltic waves (figure 7). If acid perfusion reproduces the spontaneously occurring pain and produces motor abnormalities and if there are no electrocardiographic abnormalities, the evidence becomes impressive that the symptoms are due to esophageal dysfunction and not to coronary arterial disease.

Case 2—A 39 year old housewife was admitted to The Johns Hopkins Hospital for evaluation of chest pain and shortness of breath. At the age of 13 years, she had an episode of sharp retrosternal pain radiating to the left shoulder and down the left arm; this pain recurred in episodes over a period of

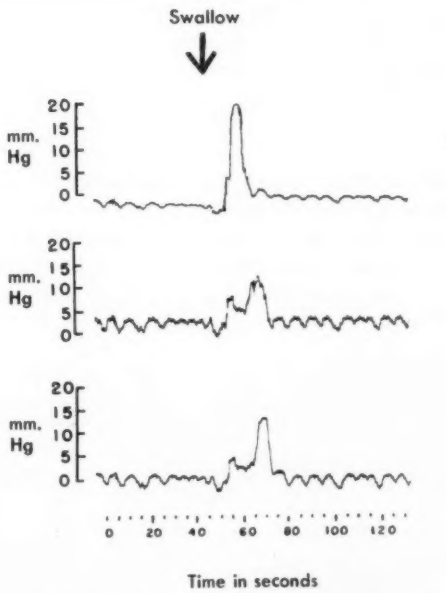

FIGURE 2. Peristalsis in the body of the esophagus. In this recording, all three catheter tips (5 cm. apart) are positioned in the body of the esophagus. The peristaltic wave proceeds down the esophagus at a rate of 2 to 4 cm. per second. The simultaneous rise in pressure which precedes the peristaltic wave is produced by the injection of the bolus into the esophagus. Peak peristaltic pressure appears first at the proximal tip (upper tracing) and passes progressively past the more distally positioned tips.

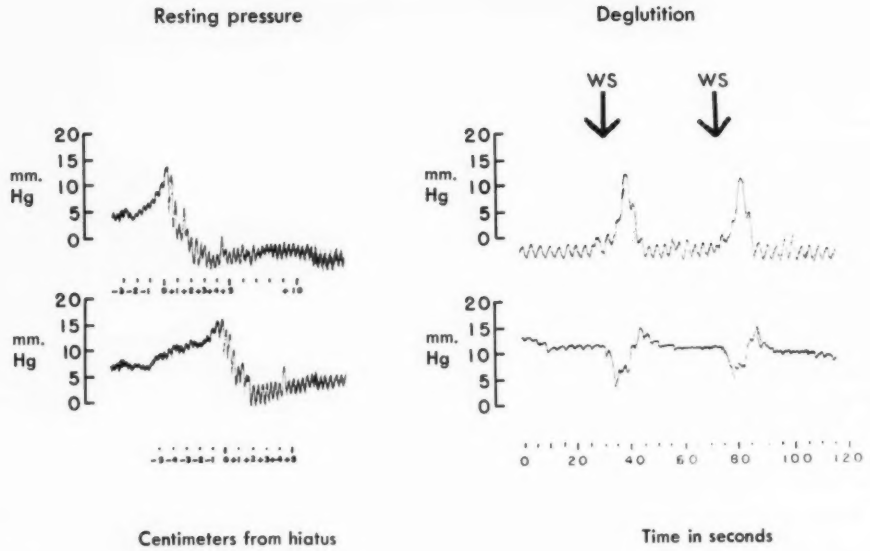

FIGURE 3. Pressure recordings demonstrating the lower esophageal sphincter in its resting state and with deglutition (recording tips 5 cm. apart). The resting pressure was recorded by steadily withdrawing tandem catheters from stomach to esophagus. The upper tracing of the resting pressure was recorded from the proximal tip, and the lower from the distal tip. The pressure in the lower esophageal sphincter exceeds intragastric pressure by 6 to 9 mm. Hg at end expiration. Following a swallow, relaxation of the lower sphincter is observed (right-hand recording, lower tracing). Normally this relaxation occurs 1.5 to 2.5 seconds following a swallow and lasts 5 to 12 seconds.

two to three years, after which she was well until five years prior to her present illness. At that time, she experienced sharp, pressing retrosternal pain radiating to the left shoulder and down the left arm. The pain was not definitely related to exertion, but the patient obtained partial relief from nitroglycerin. Numerous electrocardiograms obtained both at rest and following exercise were normal. Physical findings at the time of admission to

FIGURE 4. *Left.* Resting (closed) lower sphincter between the esophagus above and the stomach below. *Right.* Same area relaxed (open) following a swallow.

FIGURE 5. Case 1. Dilatation of the lower esophagus and "holdup" of barium at the cardia. These findings suggested the diagnosis of achalasia, but motor studies revealed peristalsis in the body of the esophagus and relaxation of the lower esophageal sphincter, thus ruling out achalasia.

the hospital were unremarkable. The hemogram and urinalysis yielded normal findings. Electrocardiograms were normal at rest and with exercise. A coronary arteriogram suggested a plaque in the left anterior descending artery. An upper gastrointestinal x-ray series was normal. Esophageal motor studies revealed a marked decrease in the resting pressure of the lower esophageal sphincter. Perfusion of the esophagus with isotonic saline did not produce symptoms. When, unknown to the patient, the perfusion solution was changed from saline to tenth-normal hydrochloric acid, sharp, crushing retrosternal pain radiating to the left shoulder and down the left arm was produced, duplicating exactly the spontaneously occurring pain. Esophagoscopic examination revealed the gross changes of esophagitis. A regimen of intensive antacid therapy was instituted, and the patient's symptoms subsided almost completely.

3. Diseases of connective tissue—Scleroderma commonly involves the esophagus.[5,6] Twenty-four of 25 patients with scleroderma were found to have a characteristic pattern of motor abnormality. This pattern consists of loss of peristalsis in the lower two-thirds to three-fourths (smooth muscle portion) of the esophagus, with normal motor activity above this level (figure 8). Later the lower sphincter becomes incompetent, and this disturbance presumably plays a role in the development of the severe esophagitis that frequently is seen in scleroderma. In several patients with scleroderma the abnormalities in esophageal motor function were discovered before abnormalities were demonstrated by routine radiologic technics.

The characteristic motor abnormality in dermatomyositis is different from that in scleroderma. Peristalsis in the body of the esophagus is normal; however, the pharyngeal

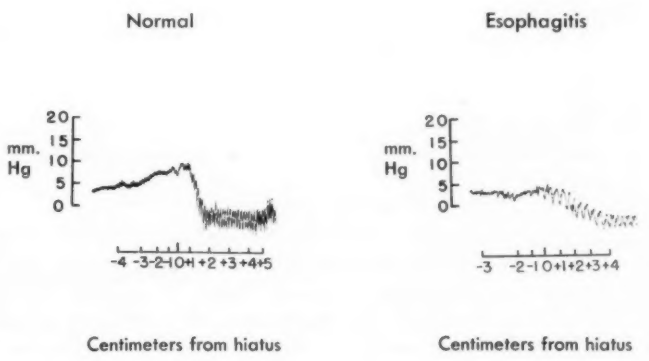

FIGURE 6. Impairment of the lower esophageal sphincter is characteristically observed in esophagitis. These recordings of resting pressure were obtained by the steady withdrawal of catheters from the stomach to the esophagus (from left to right in the tracings).

Normally, a high-pressure zone at the distal end of the esophagus is demonstrated. Virtually no high-pressure zone is observed in esophagitis, depicted in the right-hand tracing. Impairment of this key barrier to reflux may be significant in the pathogenesis of esophagitis.

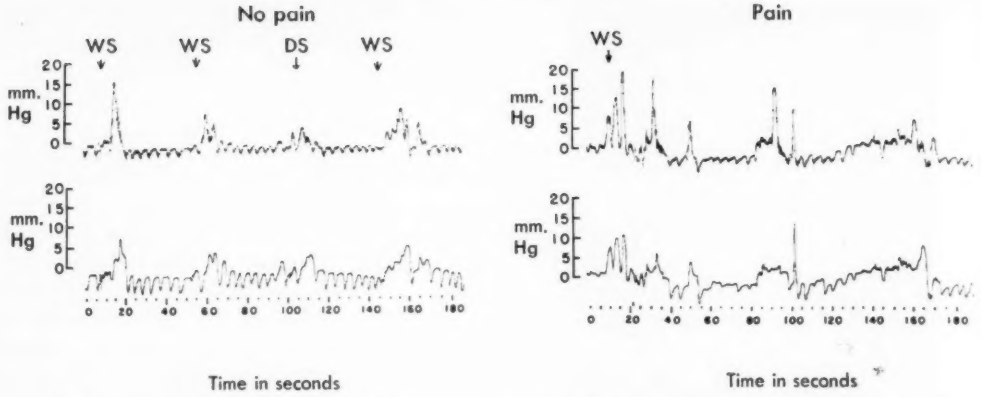

FIGURE 7. Motor abnormalities occur in esophagitis concomitantly with the symptoms of pain and heartburn. During a period when the patient was free of pain (left-hand tracings), the motor pattern was normal; progressive peristaltic contractions followed each swallow (WS, water swallow; DS, dry swallow). When the same patient experienced pain in response to perfusion of the esophagus with acid, motor abnormalities were observed, consisting of increased spontaneous (often synchronous) motor activity, increase of amplitude and duration of peristaltic contractions, and increased esophageal tone, as manifested by a rising base line. (Recording tips were positioned 5 cm. apart.)

pressure complexes may be diminished.

Case 3—A 56 year old man was admitted to The Johns Hopkins Hospital for the evaluation of ulcers on the fingertips. During the 10 years prior to admission there was progressive development of painful swelling of the fingers of both hands, cold sensitivity with blanching of the fingertips, and, more recently, tenderness and then ulceration of several fingertips. Physical examination revealed mild hypertension (188/98 mm. Hg). The patient was a muscular man. On the tips of the third fingers there were deep necrotic ulcers draining a whitish exudate; associated inflammation or tenderness was minimal. There was a brawny, indurated thickness and tightness of the skin and underlying subcutaneous tissues over the distal two-thirds of all the digits of the hands. Over the body were scattered areas of macular hyperpigmentation and vitiligo. Telangiectasis

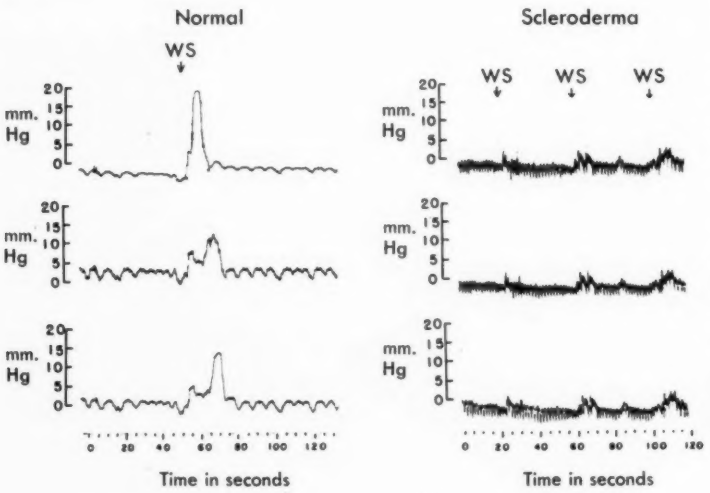

FIGURE 8. In scleroderma, characteristically there is loss of progressive motor activity in the lower two-thirds to three-fourths of the esophagus, as is depicted in the right-hand tracings.

Pressure elevation in the body of the esophagus is synchronous. This elevation is caused primarily by transmission of pharyngeal pressures through a tube that has lost its contractile function. For comparison, a normal progressive peristaltic pattern of deglutition pressures in the body of the esophagus is shown in the left-hand tracings.

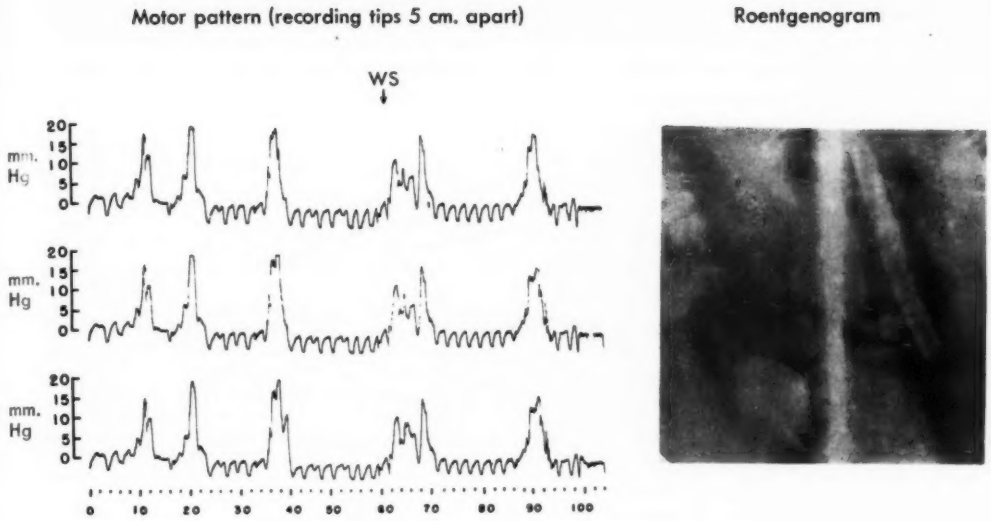

FIGURE 9. Diffuse esophageal spasm. The pressure recordings demonstrate spontaneous, uncoordinated, synchronous contractions. Pressures generated by these contractions often far exceed those normally observed. The characteristic roentgenologic picture of this abnormality ("curling" or tertiary waves) is depicted on the right.

of the lip and undersurface of the tongue was observed. The hemogram was normal. The patient was unable to concentrate urine beyond a specific gravity of 1.010. A chest roentgenogram revealed cardiomegaly. Venous pressure was normal, and an intravenous urogram was within normal limits. The electrocardiogram showed sinus rhythm with normal QRS and S-T segments, but inverted T waves in leads I, V_3 and V_5. A barium swallow yielded findings interpreted as normal. Esophageal motor studies revealed absence of peristalsis in the lower two-thirds of the esophagus with a normal motor pattern in the pharynx and upper esophagus. With the finding of this abnormal motor pattern, which we have observed as characteristic of scleroderma, this patient no longer was considered to have isolated Raynaud's phenomenon but, rather, was judged to have systemic sclerosis.

4. Diffuse esophageal spasm—The diagnosis of diffuse esophageal spasm, which may be suggested by the radiologic findings of "curling" or tertiary waves, is one that can be made with certainty only by means of esophageal motor studies. The abnormality is characterized by simultaneous, often repetitive, spontaneous contractions in the lower esophagus (figure 9). The pressures generated by these contractions often far exceed those normally observed. The underlying basis for this disturbance of motor function is unknown. The radiologic features of diffuse esophageal spasm often are intermittent, and a barium swallow may not demonstrate this abnormality. These cases generally would be detected by esophageal motor studies. Occasional cases of dysphagia without radiologic or endoscopic abnormality are ascribable to this disorder of esophageal motor function.

Case 4—A 71 year old married woman was admitted to The Johns Hopkins Hospital complaining chiefly of difficulty in swallowing of two years' duration. She had the sensation of solids (but not liquids) "sticking" at various levels, ranging from behind the manubrium to behind the midsternum. Rapid swallowing of water helped to relieve the sensation. In 1928, the patient had been told that she had a goiter, and in 1958 she underwent subtotal

thyroidectomy. In April 1957, an upper gastrointestinal x-ray series demonstrated a large hiatus hernia. Physical examination at the time of the present admission did not yield remarkable findings. The hemogram, results of urinalysis, and the electrocardiogram were normal. A large fixed hiatus hernia was demonstrated radiographically, and surgical repair was contemplated. Esophageal motor studies, however, revealed the pattern of diffuse esophageal spasm. Following the sublingual administration of 0.1 mg. nitroglycerin, the esophageal motor pattern reverted to normal for seven and one-half minutes, with concomitant subsidence of dysphagia. After the seven and one-half minute period, dysphagia recurred and then the motor pattern of diffuse esophageal spasm returned. The patient was dismissed without operative treatment, and a regimen was instituted consisting of six feedings per day, antacids, nitroglycerin p.r.n., and weight reduction. There has been significant and sustained improvement in her condition.

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Psychiatric Contributions to the Clinical Management of Plastic-Surgery Patients

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AND MILTON T. EDGERTON†

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Fifty-four of 157 plastic-surgery patients seen in a two year period had psychologic problems important to their clinical management. Case reports are presented to demonstrate the types of clinical problems and the application of psychiatric principles. A psychiatrist makes four specific contributions to the clinical management of plastic-surgery patients: identification of severe personality problems, clarification of expectations and motivations, definitive psychotherapeutic intervention, and facilitation of healthy psychologic development made possible by surgery.

DEFORMITY rarely means the same thing to the patient and to the surgeon who treats the patient. The difference in meaning can be a critical factor in surgical management. In this report we shall utilize selected case material from the full range of patients seeking plastic surgery to illustrate specific contributions that a psychiatrist can make to the clinical management of such patients.

Clinical Material

During a two year period, from November 1957 to October 1959, 157 patients seeking plastic surgical procedures were seen by the same psychiatrist (W.E.J.). Fifty-four of these patients had personality problems important to their clinical management (table 1). This total sample is composed of two subgroups: 120 consecutive patients who sought cosmetic surgical treatment and were referred for routine psychiatric evaluation as part of a research project, and 37 nonconsecutive patients with moderate or severe deformity who were referred to the psychiatrist by the surgeon (M.T.E.) because they represented "typical" or "difficult" problems in reconstructive surgery.

Forty of the 120 patients in the first subgroup were in need of psychotherapy. In 32 of these 40 cases the psychiatrist's efforts succeeded in some measure. The period of psychotherapy ranged from 1½ to 150 hours. Eight patients either refused or were unable

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WAYNE E. JACOBSON

EUGENE MEYER

MILTON T. EDGERTON

to follow the recommendations for treatment.

Ten of the 37 patients in the second subgroup have had psychiatric treatment, ranging from 1½ to 30 hours. In four additional cases, recommendations for treatment could not be implemented.

On the basis of repeated and detailed consideration of the interviewing psychiatrist's work, we suggest that he makes four types of contributions to patient care: (1) identification of severe personality problems, (2) clarification of the patient's expectations and motivations for seeking plastic surgical treatment, (3) definitive psychotherapeutic intervention, and (4) facilitation of healthy psychologic development initiated or catalyzed by surgical procedures. These contributions are illustrated in subsequent portions of this paper by typical case reports.

1. Identification of Severe Personality Problems

Most plastic surgery is elective. Aside from the usual surgical factors of hospital schedules and the surgeon's schedule, the psychologic state of the patient is important in selecting the proper time for operation. The investigative skills of the psychiatrist can be useful in preventing untimely surgical intervention.

Case 1—A 32 year old married woman sought surgical removal of a long-standing, obviously benign blue nevus on the left cheek. During the initial surgical interview her manner and speech were not unusual. The requested surgical procedure was feasible. A routine referral to the psychiatrist was made as part of a research program. Psychiatric investigation showed that the patient had a chronic, severe paranoid type of schizophrenic reaction. She had long-standing delusions of persecution and autistic preoccupations with a series of hallucinated men—including doctors—whom she felt were torturing and persecuting her. The surgeon accepted the psychiatrist's recommendation not to operate.

Gross disturbances in personality functioning are not always readily apparent; they are not found without knowledgeable questioning, and, even if known to others, may not be communicated to the surgeon.

Case 2—A prim, attractive 30 year old mother of five children sought dermabrasion for removal of chloasma. She was referred for routine psychiatric evaluation. During the interview with the psychiatrist, gross indications of a psychotic illness were noted. She had many somatic delusions. She was depressed, she cried easily, and she was unable to concentrate. She complained of insomnia and suicidal thoughts. Her home life was punctuated by her violent paranoid tirades. Because of the severity of her emotional illness, the dermabrasion was deferred and psychiatric treatment was advised. In planning for definitive psychiatric therapy, her husband was interviewed. Although he had supported her surgical quest, he was aware of her emotional difficulties and had hoped the surgeon would refer her to a psychiatrist. He had not, however, communicated this hope.

The identification of personality problems excludes some patients from surgical treatment at a time when evaluation of results is difficult if not impossible. It also can prevent exposure of a patient to a procedure that can be psychologically disastrous.

Case 3—A pretty, reserved 27 year old woman, married for 10 months, sought augmentation mammaplasty. She had been self-consciously concerned about the size of her

TABLE 1

CLINICAL MANAGEMENT OF PLASTIC-SURGERY PATIENTS, THE JOHNS HOPKINS HOSPITAL, NOVEMBER 1957 TO OCTOBER 1959; TYPE OF PSYCHIATRIC TREATMENT

	MODERATE AND SEVERE DEFORMITY	MINIMAL DEFORMITY	TOTAL
Evaluation	23	80	103
Evaluation and brief psychotherapy	2	7	
Evaluation and definitive psychotherapy	6 — 14	23 — 40	54
Evaluation and referral for psychotherapy	2	2	
Evaluation; psychotherapy refused	4	8	
TOTAL	37	120	157

breasts since adolescence. She was referred for routine psychiatric evaluation. Although presenting a façade of social adequacy, she gave a history of severe life problems. Following her mother's suicide when the patient was two years old, she grew up as a lonely, unattended, depressed child. Her father was uninterested and alcoholic. She gradually and painfully surmounted some of her handicaps. She married a concerned, protective man who was sexually impotent. Her sense of deformity represented her concerns about her adequacy as a woman and her feelings of worthlessness as a person. During the interview she mentioned her fear of surgery which, aside from the more or less expected concerns, represented her fear of becoming psychotically depressed—"where the whole horrid past would come up and hit me in the face. I don't think I could take it." She was rightly concerned whether she could cope with the changes sought and represented by her surgical quest. Uncovering, clarification and acceptance of the validity of her concerns allowed her to decide easily against operation. At a follow-up visit one year later, she appeared to be reasonably happy and reported that she had managed a pleasant and successful pregnancy. She has no further interest in having an operation on her breasts.

Comment—Patients frequently do not intrude their psychoses on others in an obvious fashion. Where the patient's expectations of the surgical result are highly colored by magical and grandiose ideas, it is clearly unwise to undertake elective surgery. In such circumstances the evaluation of results is difficult if not impossible. The surgeon's skillful technical results become lost in the patient's enduring psychopathologic state.

2. *Clarification of the Patient's Expectations and Motivations*

Clarification of the patient's expectations and motivations can contribute to appropriate decisions about surgical treatment.[1]

Case 4—A 35 year old mother of four children (figure 1) had sought a rhinoplasty five years previously but had been dissuaded from it by the plastic surgeon because of her difficulties in stating what she expected and because of her own reservations about the appropriateness of the procedure. Subsequently she was seen because she was concerned about a mole on her cheek. While reviewing her history, the surgeon asked about her old desires for rhinoplasty. The patient still had intense, mixed feelings about this and welcomed an opportunity to talk with a psychiatrist. She had six psychiatric interviews, to explore the persistence of her concerns about her appearance and her guilt-ridden indecision about rhinoplasty. Her preoccupations with her appearance and her guilty indecisiveness were character traits that influenced many areas of her life. They had developed principally out of real difficulties in coping with a disturbed, critical, paranoid mother. With

FIGURE 1. A 35 year old married woman who had a rhinoplasty and chin augmentation. Preoperative psychotherapy enabled her to decide to have surgical treatment, the results of which are subjectively satisfactory. The patient obtained significant psychologic benefit.

awareness of how these early difficulties still influenced her to be indecisive, the patient was able, without guilt, to request a feasible surgical procedure which greatly improved her appearance. Two years later, she is pleased with the surgical results and is utilizing her new concepts of herself in a comfortable and socially effective manner.

Clarification of a patient's expectations and motivations also can prevent disappointment or refixation on minor imperfections.

Case 5—A thin, dowdy, harried-appearing 27 year old housewife sought dermabrasion for severe acne scarring of the face. Her worried, tense unhappiness was apparent in her initial interview with the surgeon. She was desperately eager to secure what benefit might accrue from dermabrasion. Intellectually she accepted the limitations. A routine referral for psychiatric evaluation was made.

During the psychiatric interview she told of a harsh, socially limited, emotionally burdened childhood. Her acne had erupted during adolescence but had not been of major concern until recently. In her late teens she married a harsh, irresponsible man who became increasingly alcoholic. Their sexual adjustment was difficult and unhappy. Problems of economic, social and emotional poverty were pressing. Her marriage became increasingly unhappy, and following an episode of physical abuse she secured a divorce. Subsequently she married an older, responsible, gentle man who took good care of her and her children. Their sexual adjustment was characterized by a pleasant, lusty, erotic interchange. "I never knew it could be like that." Two months following her second marriage, she began to be increasingly concerned and self-conscious about her appearance. She developed ideas of reference and became irritable, weepy and seclusive. In spite of her severe emotional disturbances, her request for dermabrasion was accepted with the provision that psychiatric treatment be continued.

Following surgical treatment, the patient remained distressed and was disappointed with the results. The psychiatrist directed her attention to the meanings of her cosmetic concerns. Her acne scarring represented, for her, a sign of sexuality. Her reaction to her newfound sexual gratification was compounded of pleasurable satisfaction and intense, guilt-ridden anxiety, the latter arising from ignorance and being a hang-over of parentally acquired attitudes; her family's attitudes toward sex had been characterized by aversion, disgust, revulsion and punitive suppression. With

FIGURE 2. This 35 year old housewife with carcinoma of the face became psychotically depressed following removal of her eye. Outpatient electroshock therapy was lifesaving and enabled her to continue with necessary surgical treatment.

clarification and information, the patient was able to be increasingly comfortable with her sexuality. Social functioning improved, ideas of reference disappeared, and she was realistically acceptive of the surgical results.

Comment—Detailed clarification of the patient's expectations and motivations for surgery is a routine practice among most plastic surgeons. Some measure of doubt, indecision or guilt is normal for patients seeking cosmetic operations. It is helpful for the patients to air their ambivalent feelings. Unless specifically asked about them, patients do not voice their reservations preoperatively, lest they prejudice the quest for surgery. Postoperatively the patient's ambivalent feelings may emerge in the form of guilt and depressive reactions. They may also be manifested as fixations on minor imperfections in surgical results.

3. *Definitive Psychotherapeutic Intervention*

Adverse psychologic responses to the standard necessities of surgical care can interfere with good clinical management and occasionally can be life-threatening. A psychiatrist's knowledge of treatment possibilities can make a critical difference.

Case 6—An able, intelligent 35 year old housewife (figure 2) had been followed in the plastic clinic for seven years. She had had extensive operations of the face for carcinoma. A late recurrence necessitated additional surgery and finally sacrifice of an eye. At this time, this cooperative and enduring woman became depressed. Not only was she concerned about her medical condition, but she was frightened of becoming helpless and, as important, was angry with her mother, her husband and the surgeon—the persons on whom she depended. She was angry at them for their inability to perform miracles and for removing her eye. Her depression became more psychotic. She became delusional, agitated and sleepless. She was losing weight rapidly and was preoccupied with dying and suicide. Psychiatric hospitalization was refused by the patient and her husband, but the urgency of her condition continued. Arrangements were made with the psychiatric clinic for this patient to receive electroshock therapy as an outpatient. The improvement was dramatic. She responded quickly with a mood change. Delusional and suicidal thinking disappeared. She began sleeping and had a satisfactory gain in weight. This critical change in her psychologic state has been maintained for 18 months, during which time two addi-

tional surgical procedures have been performed. It has enabled her to participate constructively in her home life and with the surgeon in the lengthy and still grim battle against cancer.

Correct understanding and management of disturbed behavior require recognition and management of symbolic meanings. Unexpected surgical sequelae[2,3] often bring these meanings to light. Themes of "crime and punishment" can add to the realistic distress of pain and infection.

Case 7—A 30 year old housewife and mother of Italian extraction sought augmentation mammaplasty. A vivacious, capable woman, she had no major psychiatric symptoms. Following the surgical procedure, a severe infection developed in one breast. The patient had a slightly elevated temperature and some pain. She felt guilty about having the operation and was apprehensive about the outcome. During drainage of the infection, she had a severe anxiety reaction characterized by fears of dying, panic, restlessness, exaggerated helplessness, and a fearful apprehension of doctors and nurses. Psychiatric treatment gave meaning to her reaction. With the surgical cleanup, a frank abreaction was stimulated in which the patient re-experienced the fright associated with a psychologically traumatic tonsillectomy at the age of six years. As the pus was drained, she was overwhelmed with fear and guilt and re-experienced the uncertainty and concern she had felt at the age of four years when her baby brother died. The olfactory stimulus from the pus was directly associated (via feces) with the brother's death from diarrhea; the guilt and fright were related to the feeling that she may have caused his death. When the nurse suggested that the patient should relax and sleep, she became even more frightened and overactive. She felt that this suggestion was an indication that she was dying, for she had been told when her brother died that he was "asleep." This series of unexpected, emotionally charged responses to a surgical problem subsided with ventilation, support and insight. The patient was then able to deal with the realities of her surgical situation.

The employment of psychotherapeutic skill can be useful in coping with some of the complex problems of doctor-patient relationships. By training, the psychiatrist is alert to the significance of transference. Unconscious and symbolic determinants influence all doctor-patient relationships. Such influence is not necessarily pathologic, and frequently it is beneficial, but under some circumstances transference reactions, if not recognized, can be troublesome and disruptive.

Case 8—A successful 55 year old widow (figure 3) needed extensive facial reconstruction because of carcinoma. Her initial tense, apprehensive attitude changed following the second surgical procedure. She became psychotically depressed and had suicidal preoccupations, sleep disturbances, and a seclusive disinterest in activities and persons she previously had enjoyed. The psychiatrist was asked to see her. He recommended psychiatric hospitalization but the patient and her family refused. She did, however, initiate an outpatient psychotherapeutic relationship.

The patient had been a vivacious, capable, active woman, and a series of personal calamities had preceded her surgical problems. Eighteen months previously, her husband had been told that he had cancer. She had nursed him through his terminal illness. Following his death, there was a family squabble over the estate. For the patient, this represented a bitter, angry disappointment in her family, and she became concerned about being a failure as a mother. Her youngest daughter, with whom the patient was closely identified, married and left home. The patient then underwent surgical treatment of carcinoma of the face, which necessitated extensive reconstruction. During all this time, she had utilized physical activity and denial to deal with the emotional impact of this series of events. Her psychotic decompensation coincided with the anniversary of her husband's death, and psychologically her capacity to deny his loss was gone.

In her work with the psychiatrist, the patient discussed her feelings about the surgeon. She felt totally dependent on him but brought to this relationship an intense ambivalence, compounded of residua of previous difficulties

FIGURE 3. This 55 year old widow became psychotically depressed during extensive reconstructive surgery in the treatment of carcinoma of the face. Her depression interfered greatly with her relationship to the surgeon. Outpatient psychotherapy resolved her depression and the doctor-patient relationship improved.

with her father and her husband and unknowingly reinforced by the surgeon. This transference problem was of major concern to both the patient and the surgeon and interfered with effective communication about surgical problems. Psychotherapy was directed toward clarification of the transference with patient and surgeon, supportive management of the patient's needs for mourning, and ventilation of many of the disappointing and hostile elements of her ambivalent relationships to persons on whom she depended.

Psychotherapy has promoted effective efforts toward recovery. The patient is psychiatrically convalescent. Although additional surgical treatment is necessary, she and her surgeon are more comfortable and better able to collaborate without interference from her depression and unconscious distortion of their relationship.

Comment—Emotional disturbances are not uncommon among patients having plastic surgery.[4] Numerous psychologic issues can be represented by a patient's anatomic concerns. Likewise, residua of interpersonal events are brought by the patient to his or her relationship with the surgeon, who is participating in a crisis in the patient's life and future. Meaningful support requires not only an understanding of the patient's life situation but an awareness that the patient's investment in the surgeon far exceeds respect for operative competence. The surgeon's time is always taxed. In troublesome circumstances a psychiatrist with whom the surgeon can work comfortably can be most helpful, both as a translator as to what the patient is about and as a collaborator who by training and disposition can assist if "things really get out of hand."

4. Facilitation of Healthy Psychologic Development

Psychiatrists are likely to be more aware of the potential difficulties than of the potential benefits of plastic surgery. It is not unusual that the surgical alteration of minimal or severe deformity initiates or catalyzes a healthy psychologic change. Psychotherapy at this time can be useful in assisting patients to consolidate these changes.[5]

Case 9—A 16 year old high school girl (figure 4) had a secondary repair of harelip. She was seen by the psychiatrist because she did not know the nature of her deformity. She had been told that her scars were the result of a fall when she was an infant. The patient's father was anxiously overprotective, and the mother was defensive, uncommunicative and

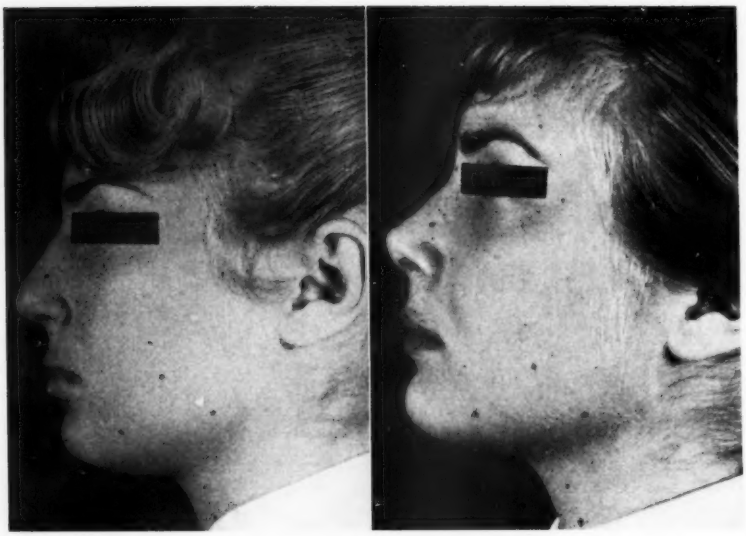

FIGURE 4. This 16 year old high school student had a secondary plastic correction of a harelip deformity. Postoperative outpatient psychotherapy facilitated healthy personality development initiated by the surgical treatment.

uncomfortable about the patient's problems. The patient, a bright, serious, introspective person, talked easily with surgeon and psychiatrist. With considerable feeling, she indicated that she felt angry and futile about her relationship with her mother. She conveyed great concern about a sense of ugliness and deformity, out of keeping with her appearance. This sense of ugliness she managed by feeling detached from participative living with her peers.

Secondary repair of the lip and reshaping of the nasal tip were very successful. Promises made by the family to inform the patient of the nature of her deformity were not kept. Six months after surgical treatment, the *patient* initiated a series of psychotherapy conferences, "because I can no longer hide behind my scar." She felt confused, depressed and unable to understand the intensity and fluctuation of her feelings toward people. Family tension was at a peak, with frequent angry exchanges between the patient and her mother and increasingly silent distance between the patient and her father. Gestures of friendship from her peers were received with quiet but haughty cynicism.

The patient reviewed with the psychiatrist her complicated relationships with her parents, including her own anger and rivalry. The psychiatrist specifically informed her of the nature of her physical problem. The patient, utilizing this knowledge, was able to talk with her mother meaningfully about their relationship and human responses to deformity. The patient inspected her relationships with her friends in a candid and courageous fashion. Episodes of depression were frequent but did not interfere with her increasingly effective performance in school and social activities.

After one year, psychiatric treatment is on an occasional "follow-up" basis. This is usually a review of progress and occasionally involves working out the meanings of some disturbing event. The patient's relationship with her family has improved. Scholastic performance is excellent, and college is anticipated. She enjoys her popularity at school without being addicted to it. Patient, family, surgeon and psychiatrist consider the results of combined treatment excellent.

Discussion

There are two major areas of medical concern in dealing with the plastic-surgery patient. One is the *anatomic deformity* existing as the consequence of genetic, infectious, neoplastic or traumatic processes. The other is

the *sense of deformity*, an intense personal experience of the patient. Because of the nature of human growth and development, the human body is inherently involved in many psychosocial problems of living.[6-8] The surgeon has no choice as to *whether* he will or will not be involved in both areas. His only choice is *how* he will be involved. Awareness that there is more involved than meets the eye, curiosity about natural phenomena, whether psychologic or anatomic, and utilization of knowledge from other medical specialties all increase the effectiveness of his intervention. Application of relevant therapeutic principles to the problem of the moment constitutes the art of medicine. Contributions from clinical psychiatry to the clinical management of plastic-surgery patients are germane to problems of diagnosis, decisions about operating, patient preparation, postoperative care, patient survival, doctor-patient relationships, and evaluation of the surgical results.

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A Training and Research Program in Medical Oncology

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Resources of The Johns Hopkins School of Medicine and Hospital and the Baltimore City Hospitals have been combined to establish a program of training and research in medical oncology. The motivation for its formulation, its purposes, and the current research and clinical activities are outlined, in the hope that other departments of medicine may be stimulated to engage in similar programs.

ALBERT H. OWENS, JR.

MORE complete understanding and control of human cancer remain the ultimate goals of innumerable individual research projects and large coordinated investigative programs. Although a great deal of descriptive data have accumulated from past observation, particularly at the laboratory level, clinically neoplastic diseases remain an ill-defined complex. Only in the rare instance do we understand something of the etiology and pathogenesis of the various ills they produce in their hosts.

Paradoxically, modern trends in scientific specialization have complicated matters somewhat by hampering a catholic appreciation of recent experimental results. Further, the investigations of neoplastic diseases in man, especially from the internist's point of view, have been pursued less vigorously than their laboratory counterparts, and the opportunities for closely correlated studies in the clinic and laboratory have not been widely available. The relative scarcity of qualified clinical investigators has been no small factor in this regard.

During the past four years, our department has been cooperating in the clinical cancer chemotherapy trials sponsored by the Cancer Chemotherapy National Service Center. As members of the Eastern Solid Tumor Group, we have compared the efficacy of several alkylating agents and antimetabolites in various clinical circumstances. We have also started the initial surveillance in humans of agents such as 5-fluorouracil, cyclophosphamide, and

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uracil and alanine mustards. The methodology involved both in the preliminary study and in the more definitive controlled therapeutic trial in this setting has been the object of a major portion of our attention. We have viewed these studies as opportunities to evaluate and improve the current principles of procedure, as well as to gather data on drug action.

The completion of such chemotherapeutic studies quite naturally brought with it the responsibility of caring for a significant number of patients with various types of cancer. While observing such a patient population, we were continually confronted by clinical syndromes of obscure origin and situations which suggested interesting investigative possibilities. An increasing awareness of the broader implications to be derived from these stimulating clinical experiences motivated the formulation of a medically oriented, comprehensive and integrated program of training and investigation in oncology.

Purposes of the Program

We believe the chief purposes of a medically oriented program of training and research in oncology such as the one we have established are as follows.

1. To acquaint qualified physicians and other closely associated investigators with the clinical and laboratory problems extant in this area and the several current approaches to their solution. Many physicians with two or three years of postgraduate experience in internal medicine have also acquired special skills and training in pharmacology, biochemistry, immunology, physiology, etc. Their potential contributions to cancer research are self-evident, and the need to encourage the best of them toward a full-time investigative career is equally clear. Most important, also, is the opportunity for laboratory-trained scientists to work in close physical and intellectual liaison with their clinical counterparts. Their associations cannot be but mutually stimulating, and their individual contributions will be complementary.

2. To expand and supplement the instruction of undergraduate medical students and house officers relative to human cancer. The hematologist classically has been responsible for the management of patients with leukemia or lymphoma. The internist presently cares for a large portion of patients with cancer, and future therapeutic advances doubtless will see him playing a more significant role, for which he must be prepared. In addition, there are compelling reasons to introduce these students and house officers to the research opportunities in this field early in their careers.

3. To develop related clinical and laboratory investigations appropriate to the available clinical material, interests and aptitudes of the investigators and existing facilities. A wide variety of problems is likely to interest a person with a background in internal medicine. Among them are the several metabolic, hematologic, immunologic and endocrine derangements secondary to the tumor-host relationship, the various pharmacologic actions and dispositions of the chemotherapeutic agents, and the possibilities centering around the causation of these diseases.

Facilities and Current Activities

Successful pursuit of such a program is predicated on the availability of significant clinical material which can be followed closely on a long-term basis, clinical facilities necessary to patient care and study, and equal facilities for training and laboratory research in close physical proximity. To these ends, we have blended certain resources of The Johns Hopkins medical institutions and the Baltimore City Hospitals.

The trainee with a background in clinical medicine can readily enter into our current clinical activities. He also may wish to enroll in a course in biostatistics, immunology or epidemiology or review his biochemistry and pharmacology. If he has not had prior laboratory training in the basic sciences and wishes to acquire this, a number of such opportunities are open to him. We would hope that during a two year traineeship each individual would complete some appropriate course work early and, later, enter into a laboratory project of his choice.

Weekly teaching rounds are made at The Johns Hopkins and the Baltimore City hos-

pitals, and the trainees see many patients in consultation. Both institutions are endowed with a wide variety of clinical material. At The Johns Hopkins Hospital an outpatient service oriented to research and training (the Growth Clinic) has been established for the long-term follow-up of selected patients with various neoplastic diseases. At the Baltimore City Hospitals a 20 bed inpatient medical oncology service has been set in operation to serve similar goals. Adequate laboratory facilities are available.

A brief description of our current research projects may serve to indicate our particular interests and illustrate several of my previous remarks.

One group of experiments is designed to evaluate the usefulness of a carcinogen-induced mammary cancer in rats as a predicting system for its human counterpart. Epithelial tumors of ductal origin arise almost invariably within a reasonable period of time in female rats treated with 3-methylcholanthrene. In general they are responsive to the endocrine manipulations known to affect human breast cancer. These circumstances suggest an obvious comparison and the possibility of a screening tool which must be proved by correlated comparison in rats and in humans.

Recent studies of the metabolism of 6-mercaptopurine (or related antipurines) in bacteria and transplantable mouse tumors have provided the impetus to another series of experiments designed to test the pertinence of the laboratory observations to the human situation. It has been shown that 6-mercaptopurine is converted to its riboside prior to the production of its pharmacologic effect and that a lack of this conversion seems to be correlated with tumor resistance. Does this or a similar mechanism pertain to human leukemia? Could one, through the completion of a relatively short biochemical procedure, predict the clinical response to administration of 6-mercaptopurine?

An attempt is being made to evaluate the interplay of disease and drug treatment on bone marrow function. The toxic effect of the administration of most known agents is depression of the bone marrow. Do repeated courses of mustard or antimetabolite treatment produce a cumulative damage to the marrow similar to that seen with whole-body x-ray exposure? Would the administration of larger doses of the drugs, made possible by marrow shielding or transfusion, produce a greater antitumor response?

Interest is increasing in the effect of neoplastic diseases and various cancer chemotherapeutic agents on an individual's immune responses. We are systematically evaluating the effect of these variables on the primary and booster responses to antigen, the persistence of isoagglutinin titers, the development and maintenance of delayed hypersensitivity responses, and, to a more limited extent, tissue transplantation.

Comment

We believe that a fuller understanding of the complexities of the neoplastic diseases will be hastened by the basic contributions of workers trained in many scientific disciplines. We would hope that in the near future more departments of medicine will be engaged in these activities.

We are obviously enthusiastic about this program, although it is still in its infancy. We have been fortunate in receiving the support of the professor of medicine, Dr. A. M. Harvey, and of the emeritus professor of pharmacology and experimental therapeutics, Dr. E. K. Marshall, Jr. We recognize, too, our good fortune in the excellent clinical material and the academic and physical facilities available to us. The timely burgeoning of the national cancer chemotherapy program provided the critical catalytic ingredient which awakened us to the almost limitless possibilities in this investigative area.

The Role of a Division of Clinical Pharmacology in a University Environment

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A brief history is given of the development and activities of the Division of Clinical Pharmacology at The Johns Hopkins University School of Medicine. The principles of its operation include continuing emphasis on methodology of evaluation of drugs, selection of study materials that are of scientific interest, pursuit of both clinical and nonclinical research problems, multidisciplinary approach, stability of support and personnel, and financial support free of restrictions.

LOUIS LASAGNA

ACADEMIC groups devoted to clinical pharmacology are as yet relatively rare in this country. Therefore, it may be profitable for some readers to learn in detail of the development and activities of one such group, the Division of Clinical Pharmacology of the Department of Medicine at The Johns Hopkins University School of Medicine.

The Division was organized in July 1954, and has grown salubriously. From the original membership of one, it has expanded so that today it includes five full-time professional members, four part-time professional members, four fellows, eight secretaries and technicians, and six nurses. The members have published 44 scientific articles or book chapters, have served on the editorial boards of such periodicals as the *Journal of Pharmacology and Experimental Therapeutics*, *Journal of Chronic Diseases*, and *Psychopharmacologia*, and have served as consultants to the National Cancer Institute, the National Institute of Mental Health, the Stanford Research Institute, the Food and Drug Administration, and the American Cancer Society.

This gratifying record of growth, service and accomplishment is in some ways difficult

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to describe historically. Chance and good luck have played important parts in assisting the Division to acquire support and first-rate personnel. Our school has been fortunate, for example, in having enthusiastic support for clinical pharmacology from both the professor of medicine, Dr. A. M. Harvey, and the professor of pharmacology and experimental therapeutics, first Dr. E. K. Marshall, Jr., and currently Dr. Gilbert H. Mudge. Also, the past decade has seen an unusual increase of interest in clinical pharmacology on the part of industry and the governmental agencies. The National Institutes of Health have supported our research efforts from the start and recently have begun to support a training program designed to turn out more clinical pharmacologists to meet academic and pharmaceutical needs. Early in our history, important support through fellowships came from E. R. Squibb & Sons and the Pharmaceutical Manufacturers Association. In addition, we have been supported steadily for a number of years by such firms as American Cyanamid Company, Burroughs Wellcome and Company, Eli Lilly and Company, The Upjohn Company, and Winthrop Laboratories, and at various times by Merck Sharp & Dohme, The William S. Merrell Company, and Smith Kline & French Laboratories.

Basic Principles

Despite some fortuitous occurrences, we believe the success of the Division also is attributable in good measure to a basic philosophy encompassed in the following principles.

1. The methodology of drug evaluation must receive continuing emphasis. Most new drugs prove to be scientifically disappointing. It is therefore extremely desirable to utilize drug studies so that at least one can harvest useful information on experimental design, technics of evaluation, placebo phenomena, and so on. Several papers published by members of the Division illustrate these "secondary gains."[1-3]

2. For the most part, the compounds we study are selected because they are of considerable scientific interest from either a theoretical or a practical standpoint. Our facilities and personnel are too limited to allow the detailed evaluation of numerous congeners of a given drug or the investigation of a compound whose early work-up fails to present an attractive rationale for its trial.

3. If reliable information is lacking in regard to older, standard drugs, particularly because of past inadequacies in methodology, it is wise to begin studies with such standards, both to provide base-line data and to test out one's system for sensitivity and reliability.

4. Facilities are needed to pursue both clinical and nonclinical research problems. We firmly believe that pharmacology is pharmacology, irrespective of the species studied, and that if one emphasizes quality of investigation there is no need for concern about "basic" versus "applied" research (whatever these terms may mean). Many problems lead naturally from bedside to laboratory, or vice versa, and we have refused to be blocked in pursuing these by reason of artificial barriers separating the laboratory bench and the bedside. This concept, of course, has been reflected in our needs regarding both space and personnel.

5. In diversity and nonconformity there is strength. The activities of the Division have stressed the importance of avoiding doctrinaire approaches in solving problems and the utility of interaction between scientists of different persuasions and backgrounds. Since no individual or discipline has a monopoly on fruitful ideas and methods, it has appeared to us to be beneficial to encourage collaboration between such groups as dermatologists and psychologists, psychiatrists and pharmacologists, clinical oncologists and immunologists. Similarly, it has been our conviction that clinical work with drugs must not be rigidly confined either to double-blind controlled trials or to "uncontrolled" probing experimentation of the "playing by ear" variety. The "either-or" fallacy is one of the most pernicious of scientific traps, and we have tried to resist its lure.

6. A clinical pharmacology unit needs stability in terms of support and personnel. We have opposed "crash program" efforts devoted to short-time evaluation of new compounds. "Pick-up teams" of personnel for specific projects of this sort usually do not work out well,

and therefore our emphasis has been on a stable nucleus of well-trained persons.

7. Financial support must be of the "no-strings-attached" variety. Governmental support from the National Institutes of Health, of course, is delightfully free of such restrictions. In our contacts with such sources of funds as the pharmaceutical industry, we have had mixed but definite success in communicating to drug-house officials the importance of unrestricted funds and our belief that the Division's activities should not be tied too closely to any one firm. We believe that it is for the most part undesirable for a university division to be a clinical testing ground for only one or two drug houses. Rather to be desired is a continuing relationship with as much of the drug industry as is feasible.

Teaching and Research Activities

The functions of the Division are in part teaching and training and in part research. The teaching responsibilities are of several types. Members of the Division participate and assist in regularly scheduled teaching exercises, such as course work in pharmacology, physical diagnosis, psychiatry, internal medicine, the "Conjoint Clinics" given weekly throughout the year to senior students, and the annual Postgraduate Course given for internists from various parts of the country. In addition, we conduct special teaching exercises such as electives in psychopharmacologic technics, cancer research, and the methods of clinical pharmacology for medical students; a training program for fellows in clinical pharmacology;[4] and brief training courses for members of the pharmaceutical industry, individually or in small groups.

Our research is, again, of several types. A certain amount of research originates completely within our own group and is performed with our own facilities and little or no help from other persons or groups. This work is of both clinical and nonclinical nature and involves such areas as cancer chemotherapy, analgesic and hypnotic drugs, tranquilizers, and behavior. In addition, we participate in joint enterprises with other persons or groups, at times initiated by us and at times initiated by them. For example, a continuing program in the evaluation of analgesic compounds is conducted in close collaboration with the Anesthesiology Department at the Baltimore City Hospitals. We have collaborated fruitfully with psychiatrists at Springfield State Hospital, Sykesville, Maryland. We are part of a seven hospital cooperative unit (Eastern Solid Tumor Group) concerned with the evaluation of anticancer drugs. Finally, we serve in a purely advisory capacity to people in our environment who come for advice in regard to the choice of a compound for study, toxicity data, protocol design, analysis of results, and so on. Thus we may be consulted by dermatologists in regard to an acne study, by allergists in regard to a hay fever experiment, or by pulmonary specialists in regard to a chronic bronchitis study with prophylactic antibiotics.

In stimulating and carrying on research, the Division has served as a "middleman" for forwarding information from the pharmaceutical industry to investigators and vice versa. Many drug houses, aware of this role, now keep us abreast of interesting developments concerning new compounds, since we often are in a position either to conduct experiments with the compounds or to interest others in our community in studying the drugs. At times we have also served a useful function in obtaining funds from the pharmaceutical industry or from governmental agencies for the initiation of study groups in our hospital environment or for the support of already established groups.

Publications

The breadth of activities of the Division may be suggested by an analysis of the publications that have issued from the group in the past six years. A partial list of the journals in which articles have appeared would include: *American Journal of Physiology, Anesthesiology, Bulletin of The Johns Hopkins Hospital, Cancer Research, Journal of Abnormal and Social Psychology, Journal of Chronic Diseases, Journal of Clinical Investigation, Journal of Comparative and Physiological Psychology, Journal of Experimental Analysis*

of Behavior, Journal of Pharmacology and Experimental Therapeutics, Psychopharmacologia, Quarterly Journal of Studies on Alcohol, and *Science.* Approximately one-fifth of these papers have concerned general methodological problems of clinical trials, placebos, use of normal subjects, etc. Approximately one-third of the articles deal with clinical trials of various sorts, including research on hypnotics, adjuvant therapy in pneumonia, narcotics, alcoholism, cancer and diuretics. About 10 per cent are concerned with summaries and reviews of the available literature on pharmacologic topics. Over one-fourth of the papers deal with "basic" research of a kind not closely related to clinical problems. Examples of this type of research would be the synthesis of glucose by the kidney,[5] the effects of aggregation[6] and temperature on amphetamine toxicity in mice, escape-avoidance behavior in rats,[7,8] experimental "fear" experiments in man,[9] the thyroid state and thermoregulatory behavior in the rat,[10] importance of the thyroid in acute and chronic effects of amphetamine in the rat,[11] and the effect of cold acclimatization on behavior[12] and on response to drugs.[13] The research currently in progress continues to strive for an appropriate balance between clinical and nonclinical studies, and for a diversity of experimental approaches to pharmacology, physiology, biochemistry and pathology.

Conclusion

This, then, is a brief history of one clinical pharmacologic unit. To us, the record is encouraging and most promising for the future. Applicants to the Division for fellowships increase both in number and in quality as the years go on, indicating a highly healthy development in the nationwide orientation to clinical pharmacology. We believe our record can be matched or excelled in many places throughout the country and look forward to the day when divisions of clinical pharmacology will be so well established in university centers throughout the land that an article such as this will seem strangely anachronistic.

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Aural Atresia: Anatomy and Surgery

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A new operative technic for the treatment of aural atresia is described which has been used in the last five patients with this anomaly treated surgically at The Johns Hopkins Hospital. All five patients attained serviceable hearing, and in two the hearing level is better than 20 db for the speech frequency range. The operation consists of creation of a tympanic membrane and construction of a functional sound-conducting system, with maintenance of the ossicular chain, even though deformed.

The great majority of cases of aural atresia are suitable for surgical treatment. Aural embryology, pathology and pathophysiology are reviewed.

GEORGE T. NAGER

FOR the patient with aural atresia, the establishment of useful hearing is the most desired result of any operative procedure; for the surgeon, it often is the most difficult to attain. An operative technic which has produced good hearing in five successive patients with osseous atresia of the external auditory canal is described herein.†

The best basis for comprehending the problems encountered in aural atresia is knowledge of the embryology of the ear. A brief review of the normal development of the structures concerned is therefore appropriate.

Embryology

Early in the third week of intrauterine development, a vaguely marked thickening of the superficial ectoderm may be observed on either side of the still-open neural plate. This thickening, at the level of the developing myelencephalon, is the beginning of the auditory placode which invaginates during the fourth week to form the auditory pit and, later, the auditory vesicle (figure 1). The auditory vesicle thereafter differentiates into the vestibular and cochlear portions of the membranous labyrinth. By the early part of the third em-

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†An address describing the operative technic and three of the five cases was presented at the Congress held at the Gill Memorial Eye, Ear and Throat Hospital, Roanoke, Virginia, April 6, 1959.

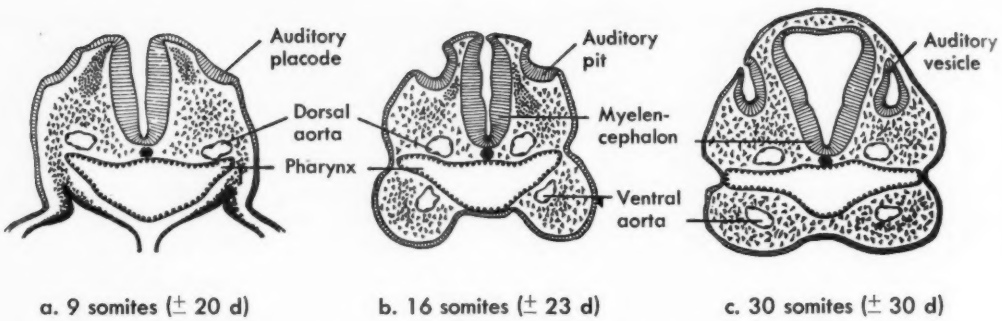


FIGURE 1. Schema of the formation of the auditory vesicle as seen in cross sections of young human embryos.

Modified from Arey, L. B.: In Patten, B. M.: Human Embryology. Ed. 2. New York, The Blakiston Division, McGraw-Hill Book Company, Inc., 1953.

bryonic month the vestibular and cochlear portions have almost an adult configuration, and by the end of this month they are completely differentiated except for part of the organ of Corti in the apical turn. While the membranous labyrinth has been taking shape, there has been a gradual concentration of mesenchyme around it, and by the time the epithelial part of the labyrinth has assumed approximately its definite form, the surrounding mesenchyme has been transformed into cartilage, separated now from the membranous labyrinth by the perilymphatic space. The cartilaginous capsule subsequently is converted into bone by the spreading of multiple centers of enchondral ossification.

At the same time that the inner ear is being developed, the middle ear and the outer ear (and, with them, the sound-conducting system) also are taking shape. On the outside of the embryonic head, between the first and second branchial arches, a branchial groove develops opposite a corresponding outpocketing of the pharynx. The first branchial groove is destined to become the outer part of the external auditory canal, the inner portion not being formed until the sixth or seventh fetal month. Toward the end of the second fetal month, a solid epithelial cord grows inward from the primitive meatus, ending in a disklike extension that lies in close proximity to the epithelium of the developing tympanic cavity, and is separated from it only by a thin layer of connective tissue destined to become the fibrous layer of the tympanic membrane. This epithelial cord begins to canalize only in the seventh fetal month, first at its medial end, forming the outer surface of the tympanic membrane, and then proceeding outward to open into the primitive meatus. Arrest of development late in fetal life, therefore, occasionally may result in an atresia near the isthmus but with a well-formed tympanic membrane and middle ear ossicles, and a pouchlike meatus adjacent to the tympanic membrane filled with epithelial debris.

The dorsal end of the first pharyngeal pouch, through gradual expansion, becomes in succession the eustachian tube, the tympanic cavity and the extensions of the latter, namely, the epitympanic recess, the antrum and the air cells. The entodermal layer of the pouch becomes the epithelium of the mucous membrane of the developing middle ear. The auditory ossicles, which likewise are constituents of the middle ear, are derived from cartilaginous supports of the branchial arches. Malleus and incus are derived from Meckel's cartilage of the first branchial arch which also forms the mandible. The stapes has a dual origin. The annulus stapedialis, the main constituent of the ossicle, is a derivative from Reichert's cartilage of the second branchial arch; the lamina stapedialis is a derivative from the otic capsule. The muscles and ligaments of the middle ear which are associated with the ossicles arise from the mesoderm in which these cartilages are embedded.

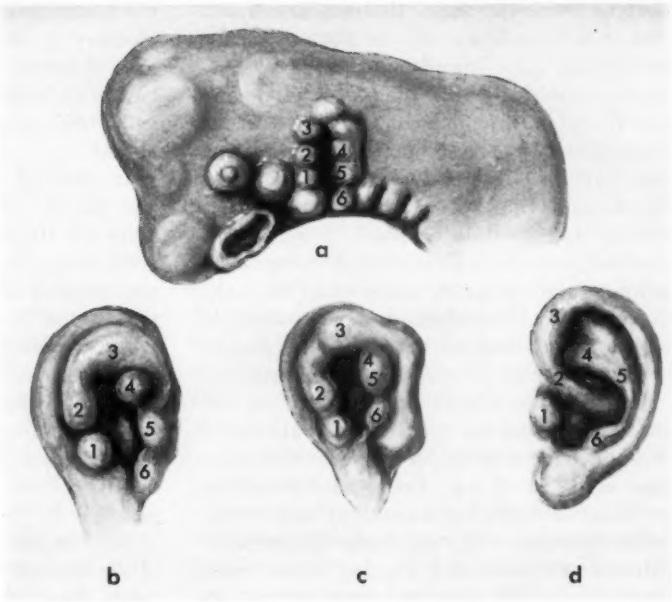


FIGURE 2. Development of the human auricle.

a. 11 mm.

b. 13.5 mm.

c. 15 mm.

d. Adult.

Partly after His, W. in Arey, L. B.: Developmental Anatomy. Ed. 6. Philadelphia, W. B. Saunders Company, 1954.

The epithelium at the depth of the first branchial groove is separated from the entoderm of the first pharyngeal pouch by mesodermal tissue. Together, these three layers of the primordial closing plate later form the tympanic membrane which separates the external ear from the middle ear.

The auricle is formed by growth of the mesenchymal tissue flanking the first branchial groove. At about the sixth week, six knoblike evaginations appear, some from the mandibular and some from the hyoid arch tissues (figure 2). The coalescence of these tubercles, by the third month, and their further development mold the pinna of the ear, the tragus coming from the first branchial arch and the remainder of the auricle from the second arch. Where the hillocks from these two arches join, just above and in front of the meatus, an epithelial-lined pit occasionally may persist into adult life as a congenital preauricular cyst or fistula.

Malformations of the outer and of the middle ear result from disturbances in development. Disturbance in differentiation of the first and second branchial arches may result in anotia, microtia, positional anomalies, and persistence of a cleft. Failure of the first branchial groove to develop may cause atresia or stenosis of the external auditory meatus. Failure of the first branchial arch to differentiate may result in aplasia, malformation, distortion or fusion of malleus and incus. Malformations of the stapes are the result of developmental failure of the second branchial arch or of the otic capsule, or both. The anomaly may involve the footplate of the ossicle, the stapedial arch, or both. Developmental anomalies of the stapes may accompany malformations of the incus and malleus, of the tympanic membrane, and of the external ear, but more often they occur independently. Thus, cases of isolated "congenital stapedial ankylosis" are not too uncommon. Recent histologic studies of the temporal bones from a patient with so-called congenital stapedial ankylosis, however, revealed that the fixation of the stapes was the result of lack of differentiation and separation of the lamina stapedialis from the otic capsule and that it was not caused by ankylosis of a previously normal, mobile stapedial footplate.[1]

The development of the membranous laby-

rinth, a derivative from the ectodermal otocyst, is independent of the development of the middle ear and sound-conducting system, which are derivatives of the branchial apparatus. Therefore it is understandable that in the majority of cases of impairment of hearing due to congenital malformations only the sound-conducting system or only the neurosensory apparatus is involved. Simultaneous involvement of both parts of the hearing mechanism is the exception rather than the rule. Combined malformations involving all three portions of the ear are very rare and usually have been observed in nonviable infants.

Furthermore, it is no longer surprising that malformations of the ear frequently are found to be associated with the various malformations of the head, e.g., Franceschetti-Zwahlen or Treacher Collins syndrome of mandibulofacial dysostosis. This syndrome includes an outward and downward slanting of the eyes, notched lower lid, short mandible, agenesis or deformity of the auricle, bony meatal atresia, and malformed malleus and incus.

Pathology

The more severe forms of congenital auricular deformation are always associated with meatal atresia, whereas meatal atresia may be seen occasionally in a patient with an otherwise normally configurated pinna.

An atresia of the meatus may be membranous or osseous. The membranous form is less common. It is characterized by a rudimentary cartilaginous canal which is separated from the middle ear by a plate of dense connective tissue. In the osseous form of meatal atresia, the bony portion of the external meatus is absent and a solid plate of compact bone is found in the region where the tympanic membrane would normally be located (see figure 5a). Osseous meatal atresia is always accompanied by a malformation of the middle ear, which varies in degree. In mild malformation the tympanic cavity is almost of normal size; the eardrum and the auditory ossicles are more or less deformed. In more severe malformation, which accounts for the majority of cases, the tympanic cavity is reduced in size; a mass of compact bone replaces the tympanic membrane; the ossicles are rudimentary or partially absent. In the highest degree of atresia of the middle ear the tympanic cavity has just a small slitlike lumen, and in very rare instances it may even be totally absent.

In marked malformations of the external and middle ear there is a tendency toward scant or absent pneumatization of the temporal bone. Also, the facial nerve occasionally may take an abnormal course within the temporal bone. It may lie uncovered within the tympanic cavity; it may emerge onto the lateral surface of the skull, following the dura of the middle cranial fossa or along a level and in the area where normally the floor of the external auditory canal would be; and it may be hypoplastic, causing a congenital facial paresis.

The mechanism of developmental anomalies of the branchial apparatus is not clear. Only rarely does a family history suggest a hereditary tendency. Unilateral atresia is somewhat more common than bilateral atresia. In unilateral atresia it is not unusual for the other ear to have a less severe malformation, with a small meatus and hypoplastic tympanic membrane or an anomaly of one or more auditory ossicles. The developmental failure present in any particular instance depends on the age of embryonic life at which normal development was arrested and on the portion of the branchial apparatus involved.

Pathophysiology

Microtia and congenital atresia are noted immediately or soon after birth, and attention is focused first on the deformity rather than on the hearing problem. If the malformation is unilateral, the hearing problem becomes of secondary importance; the impairment of hearing is hardly noticed, provided that hearing in the opposite ear is essentially normal. Clinical and histologic investigations have revealed that aural atresia is rarely associated with loss of cochlear function in a viable infant. In typical cases, therefore, hearing tests show a conductive type of hearing impairment and, quite characteristically, often relatively good hearing of the spoken voice. Even

in bilateral atresia, the spoken voice frequently is understood quite well when it is loud enough, and speech development is not necessarily impaired severely. These children, therefore, do not become "deaf-mutes" in the true sense of the word.

General Management

Reconstructive surgery is justified when in all probability lasting success can be expected. The aim of the operative procedure is to give the patient serviceable hearing which corresponds to a speech hearing level within 20 or 25 db of the normal ear. Such an improvement will give the patient the benefit from binaural hearing with greater ability to localize sound, understand speech in the presence of noise, and comprehend conversation from both sides. The surgeon's decision should be based mainly on two factors: the cochlear nerve function and the anatomy of the ear. After clarification of these factors, he must then determine the appropriate time for the procedure.

Determination of the cochlear nerve function, or cochlear reserve, can be done with great accuracy at the time the child is ready for surgical treatment. In bilateral atresia, the child's response to air-borne sound, his vocabulary as developed by amplification methods, and his responses to pure tones and speech afford a good measure of function of the inner ears. In unilateral atresia, determination of the cochlear reserve is obviously much easier.

Long before the time of surgical treatment, however, hearing can be evaluated by the methods of the Ewings and Whetnall, by psychogalvanic skin resistance and potential audiometry, and, in the older child, also by the peep-show or the play audiometry methods. Early determination of cochlear nerve function is most important in bilateral atresia, because auditory training should begin in the first year of life. This is the period when normally the hearing child is listening in preparation for speaking. Constant repetition of sound enables the cortical auditory centers to develop discrimination. As a result, the auditory association areas build up a store of engrams of sounds associated with their meanings, and gradually more complicated sounds such as speech are recognized and understood. During the same period, the child is gradually learning to control the muscles of articulation and to imitate sounds. Thus, speech gradually is being developed. Since the ability to acquire auditory discrimination diminishes as the child grows older, auditory training should begin in the second half of the first year of life in the presence of bilateral atresia with a marked conductive hearing loss. In those occasional cases of bilateral atresia combined with malformation of the head, additional factors such as the child's intelligence and personality must be considered. Aural rehabilitation then becomes much more complex and its success depends greatly on the patient's mental deficiency.

The appropriate way to study the anatomic relationship preoperatively is by roentgenologic examination. The lateral projection of the temporal bone furnishes valuable information about size and cellular structure of the mastoid portion and about position and configuration of the temporomandibular articulation. If the mastoid process is well pneumatized, it is quite likely that a middle ear cavity and ossicles are present. If a meatal atresia is partly or totally fibrous, the presence of ossicular tissue may be faintly indicated in the Schuller, Mayer or Owen projection. If, however, the area of the tympanic membrane is represented by an osseous plate, visualization of ossicular tissue is impossible in these views. When the patient's head is brought into the Stenvers position, if malleus and incus (though deformed) exist, their common structure or their heads may be projected into the shadow of the vestibule or into the upper half of the tympanic cavity, immediately beneath the shadow of the ampullar end of the lateral semicircular canal. In the symmetric axial projection, also known as Rundstroem IV position, the external meatus, attic and auditory ossicles usually are best visualized.

A radiograph may demonstrate the presence of a malleus and incus but it does not indicate anything about their functional mobility; nor does their absence in a radiograph necessarily mean that they are not present.

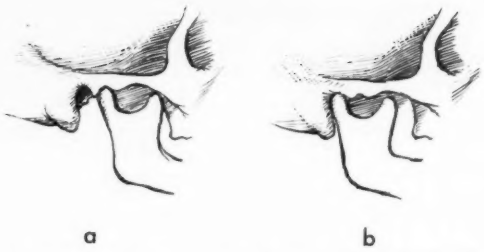


FIGURE 3. a. Normal relation of temporomandibular joint to the ear, with an external auditory meatus.

b. Osseous meatal atresia. Note the posterior position of the mandibular condyle.

The degree of differentiation of the auricle is perhaps the most reliable indication of the probable severity of the malformation of the middle ear. An absent or microtic auricle indicates arrest of development of the branchial apparatus prior to the third month of embryonic life and the probability of an aplastic or rudimentary tympanic membrane and partial absence or malformation of the malleus and incus. On the other hand, if meatal atresia is associated with a well-formed auricle, the chances are greater that there is at least a partially movable tympanic membrane and a fairly well-formed mobile malleus and incus.

In bilateral meatal atresia, reconstructive surgery is indicated when there is evidence of good cochlear function and when a middle ear cavity and possibly an ossicular structure can be identified on the roentgenogram. In most instances, the anatomic relationship and cochlear reserve are quite similar in the two ears, and for that reason it is immaterial which side is operated on first. When possible, the operation should be performed when the child is about six or seven years old. This appears to be the earliest suitable time, for the following reasons. At birth the tympanic cavity has almost an adult configuration except for the position of the tympanic membrane. The mastoid process, however, does not yet exist. Its development and pneumatization begin shortly thereafter. By the end of the sixth to seventh year of life, the entire mastoid process usually is pneumatized. Although growth of the temporal bone continues until the end of the second decade of life, the anatomic relationship of the middle ear and its structures does not change enough to alter significantly a sound-conducting system constructed at the age of six or seven years.

Since unilateral aural atresia with normal hearing in the other ear does not present an urgent hearing problem, surgery may be postponed until the patient has reached adolescence. However, consideration should be given to the advantage of binaural over monaural hearing, and for this reason one might be inclined to operate earlier.

Technic of Surgery

After the suitability of surgical treatment has been established, one must decide on the surgical procedure. Various approaches to the problem of aural atresia have been described, and the literature on this subject is quite extensive. The underlying principle of operative treatment is reconstruction of a sound-conducting system with an effective impedance-matching mechanism. Such a system includes an air-containing middle ear cavity closed by a movable membrane in contact with a freely movable ossicular chain or stapes. This tympanic cavity must have connection with the nasopharynx by a functioning eustachian tube. The cochlear fenestra also must be intact.

Correction of membranous meatal atresia associated with a functioning tympanic membrane and ossicular chain does not present any particular surgical problem. The postoperative result in such instances frequently is elimination of the air-bone gap. In contrast, osseous meatal atresia, the more common form, involves a number of technical problems. Either a thick, solid plate of bone is found in the region where the tympanic membrane normally would be located, or an osseous atresia plate with a small portion of a rudimentary tympanic membrane is found. The bony portion of the external meatus is absent and the region is filled with spongy bone. The condyle of the mandible frequently lies against the mastoid process (figure 3). The osseous form of meatal atresia also is invariably accompanied by a malformation of the middle ear, and the most frequently observed

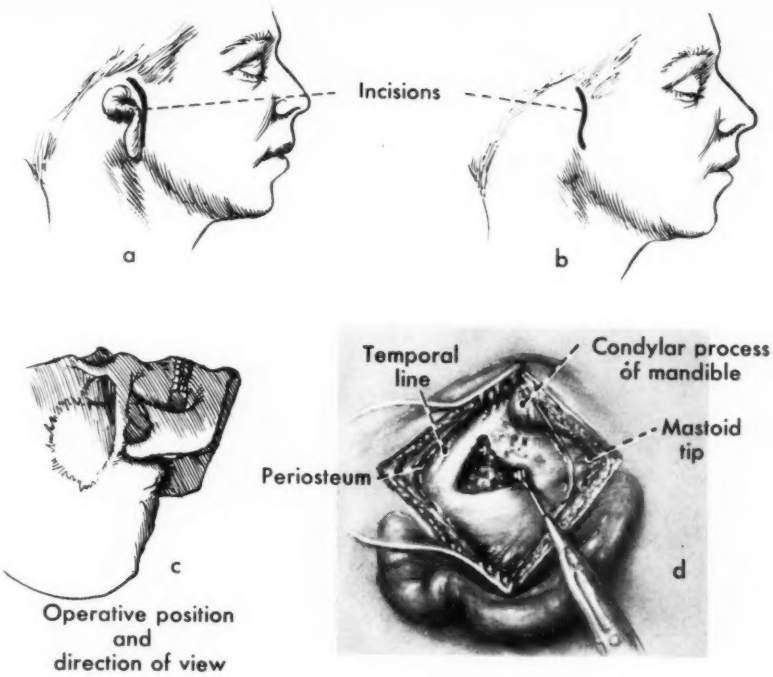


FIGURE 4. Surgical correction of congenital osseous meatal atresia.

a. Line of incision in grade 2 microtia.

b. Line of incision in anotia.

c. Position of head for operation.

d. Exposure of mastoid cortex showing the landmarks.

malformation is the one characterized by a tympanic cavity of reduced size and by rudimentary, deformed or partially absent auditory ossicles.

The majority of cases of congenital meatal atresia in which operation has been performed at The Johns Hopkins Hospital within the past three years have been of the osseous type. A new surgical technic has been developed which overcomes most of the problems. This procedure is the logical outgrowth of modern surgery of the middle ear based on the present concept of the physiology of sound conduction. The technic, to be described, has resulted in serviceable hearing in every case in which it has been used.

Incision—1. If the auricle, even though hypoplastic or deformed, is not located in an abnormal anterior and inferior position with respect to the middle ear, the primary incision is made anterior to the pinna (figure 4a). The correct position of the incision is determined by the temporomandibular joint, the root of the zygoma, and the anterior border of the mastoid process. The line of the incision greatly resembles the usual endaural type.

Exposure—2. After the mastoid cortex is exposed, certain landmarks are identified: anteriorly, the root of the zygoma and the posterior wall of the glenoid fossa, and inferiorly, the mastoid tip. Superiorly, an intimation of the temporal line may be seen, indicating the level of the floor of the middle cranial fossa. More toward the center of the mastoid cortex, a group of vascular channels occasionally is observed, suggesting the position of an antral cavity (figure 4d).

Antroatticotomy—3. If the roentgenogram reveals normal pneumatization, the mastoid cortex is removed first over the area of the

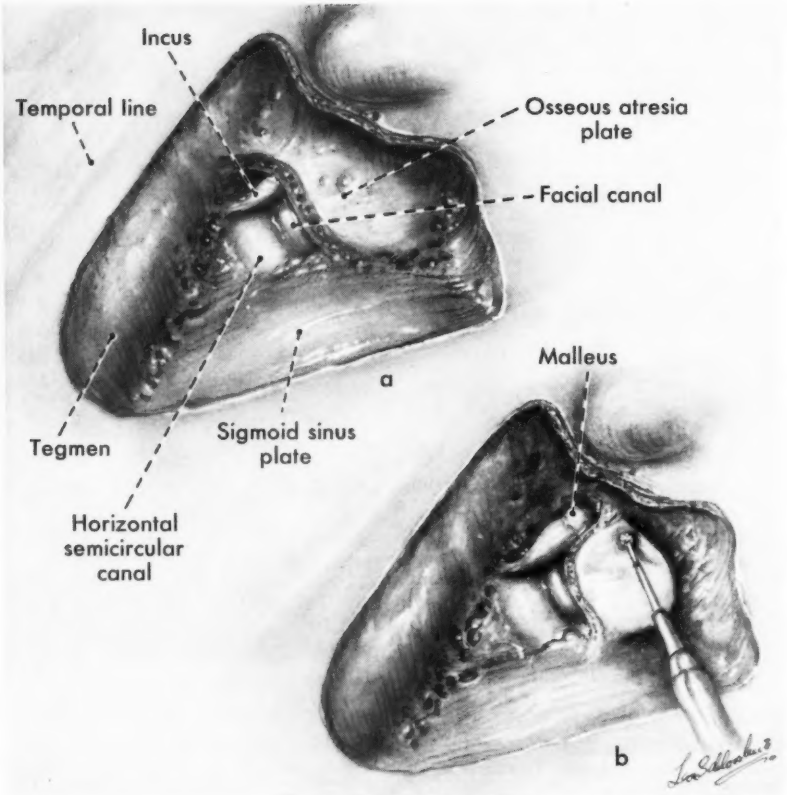


FIGURE 5. Antroatticotomy with exposure of prominence of lateral semicircular canal, upper descending portion of the facial canal, short crus and body of incus, and head of malleus.

a. External auditory meatus is constructed; the osseous atresia plate is skeletonized.

b. Modification of osseous atresia plate to dimensions of future tympanic membrane. Thinning out of central part of atresia plate.

sinodural angle. Exenteration of the underlying mastoid cells then enables identification of the lateral sinus and of the floor of the middle cranial fossa. Thereafter, the mastoid antrum is exposed and the lateral semicircular canal identified.

If the mastoid process is known to be sclerotic, the same approach is used but, since there may be few or no cells directly underlying the mastoid cortex, the dural plate beneath the cortical bone of the squama must first be uncovered. From there, the dura is followed downward and medially to the sinodural angle. Thence, the mastoid antrum and the horizontal canal are exposed in a posterior-to-anterior direction.

4. The aditus and attic then are opened widely to expose the incus and malleus fully. These ossicles, besides being deformed, frequently are located in an abnormal anterior position (figure 5a and b). This exposure enables better visualization of the tympanic portion of the facial canal in many instances. Exposure of the attic is done with great care not to dislocate the auditory ossicles from their attachments.

Construction of the auditory meatus—5. The external auditory meatus is constructed

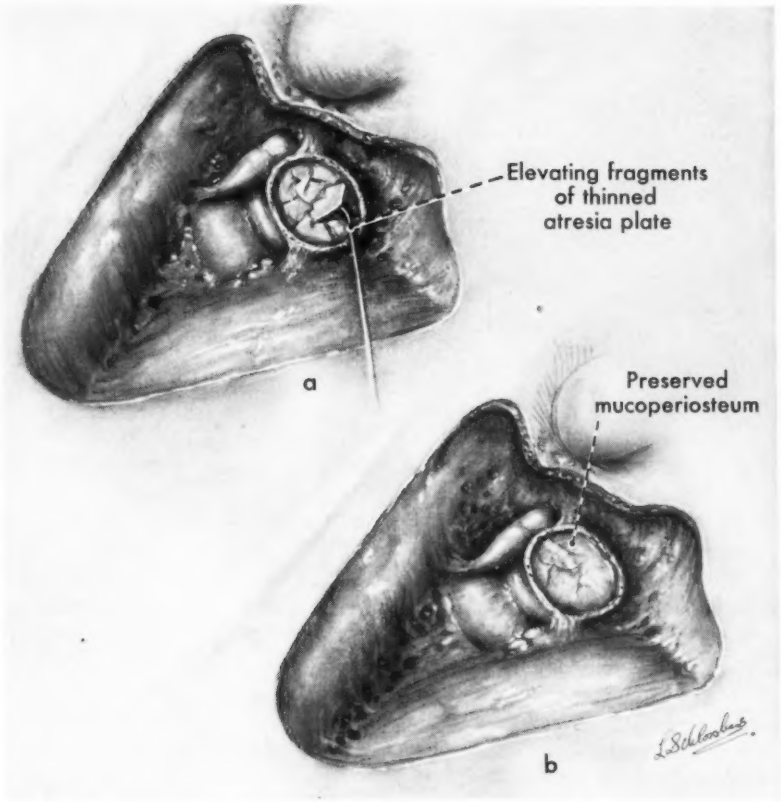


FIGURE 6. The central portion of the atresia plate has been reduced to a very thin layer of osseous tissue.

a. This osseous lamella then is fractured and the pieces are carefully elevated and removed, leaving but a peripheral osseous rim and the vascularized mucoperiosteum.

b. Vascularized mucoperiosteum to which the malleus is attached.

to about twice the size of the adult meatus by removing the spongy osseous tissue lateral to the atresia plate, between the root of the zygoma above, the posterior wall of the glenoid fossa in front, and the upper descending portion of the facial canal behind.

Construction of the tympanic membrane—6. The osseous atresia plate then is skeletonized and its usually irregular lateral aspect is smoothed down (figure 5a). The central portion of the plate then is thinned and removed, leaving only a narrow circular peripheral osseous rim (figure 5b). In removing this bone, great care is taken to preserve the layer of middle ear mucosa and periosteum (mucoperiosteum) on the inner side of the atresia plate. To achieve this, the last tissue-paper-thin layer of bone is gently fractured in the center without depressing fragments into the tympanic cavity. The fractured fragments, still attached to the underlying mucoperiosteal membrane, are gently elevated and dissected away from the mucoperiosteum by means of adequately angulated fine dissecting instruments (figure 6a). This removal begins in the center and proceeds toward the peripheral osseous rim, with great care to leave the mucoperiosteal membrane intact (figure 6b).

The preservation and utilization of this thin mucoperiosteal membrane are the most im-

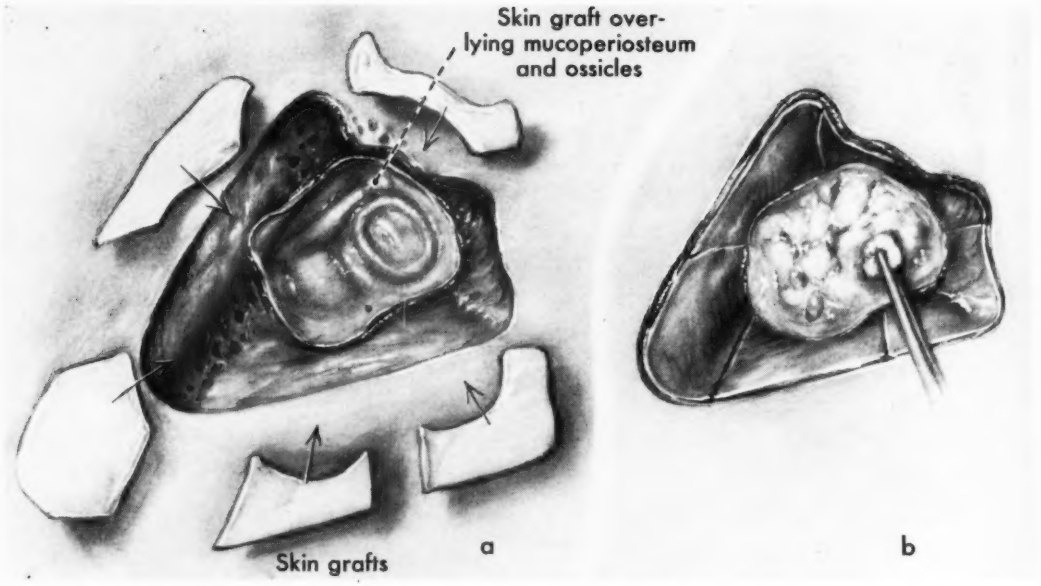


FIGURE 7. a. A full-thickness skin graft is adapted to the vascular bed of the mucoperiosteum, thus forming a "three-layered" tympanic membrane. This skin graft also covers the attic, facial canal, lateral semicircular canal and medial wall of the antrum. Additional segments of full-thickness skin graft are shaped and placed around the main graft in such a manner as to cover the remainder of the cavity wall.

b. "Formed drops" of GELFOAM® soaked in plasma and penicillin are used to maintain an even "hydrostatic pressure" on the grafts.

portant factors in the success of the entire operation, especially with respect to hearing. The malleus is already attached to this mucoperiosteal membrane, so it is not necessary to disturb the ossicular chain, which, even though distorted, can serve well to conduct sound to the inner ear. This mucoperiosteal layer, which is suspended in the circular bony frame, also provides a vascularized base for a thin full-thickness skin graft and forms the middle ear surface of the completed tympanic membrane. Thus, the newly built tympanic membrane has become a three-layered eardrum with a mucosal and a fibrous layer from the mucoperiosteum and an epithelial layer from the skin graft.

Mobilization of the ossicular chain—7. In those instances in which the head of the malleus is still attached to the anterior wall of the tympanum, the head of the malleus must be freed by removing the surrounding bone from the posterior wall of the glenoid fossa. When malleus and incus thus have been freed from all abnormal adhesions, the incudostapedial articulation is examined and the mobility of the stapes within the oval window tested.

The niche of the round window, particularly its configuration, is examined thoroughly and the secondary tympanic membrane inspected. At times it may be difficult to bring the round window niche into view. The mucosal layer of the future eardrum then has to be elevated slightly or incised posteriorly and inferiorly. If function of the vestibular and cochlear fenestrae is intact, no further surgery is necessary within the middle ear.

Thin full-thickness skin grafts taken from the groin or elsewhere are used to build up the tympanic membrane, to close the middle ear space, and to outline the purposely small mastoid cavity (figure 7a and b).

Very rarely, the stapes may be fixed in the oval window. If mobilization or replacement of the stapedial footplate is impossible for ana-

tomic or other reasons, the deformed malleus and incus are removed and the round window carefully investigated. In the presence of a normal cochlear fenestra, the operation may be terminated by fenestration of the lateral semicircular canal in the usual location with subsequent closure of the fenestra with a skin graft. Occasionally it may be advisable to perform the fenestration on the lateral semicircular canal in a second stage.

Reconstruction of a congenitally deformed or absent auricle—While construction of the external meatus, middle ear and sound-conducting system should be undertaken only by an aural surgeon well experienced in this and all aspects of modern ear surgery and thoroughly familiar with the present concept of sound conduction, in general the construction of a deformed or absent auricle may be advantageously left to the plastic surgeon who has had experience with this difficult problem.

If there is only a meatal atresia and the auricle is of normal size and configuration, there is no problem with respect to plastic surgery other than the creation of an adequate entrance to the small mastoid cavity. However, in the presence of a moderate to severe deformity of the auricle, reconstructive surgery of the pinna may be the next step in the rehabilitation of the patient.

Numerous technics have been developed and reported to correct the varying grades of microtia and to build the entire auricle in patients with congenital absence of the pinna. The technical problems here are entirely different and concern primarily the plastic surgeon, and hence it is outside the scope of this communication to discuss indications for these procedures, to enumerate the various technics, or to evaluate the operative results. The reader is referred to the pertinent literature. Leaving the technical details of reconstruction to the plastic surgeon, the point which remains to be emphasized is proper timing of such procedures with due regard for the physiology of hearing.

If total operative construction of the auricle is not indicated or desired, a prosthetic ear is made. To those of us who have seen good moulages, the cosmetic result with prostheses still seems to exceed the best result observed with a multiple-stage reconstruction.

Regardless of how much plastic repair is required in a particular case and what surgical technic is used, *improvement of hearing must precede plastic repair in unilateral and in bilateral forms of aural atresia suitable for construction of a sound-conducting system.* And it should be remembered that the great majority of patients with such developmental anomalies are suitable for hearing improvement by surgery.

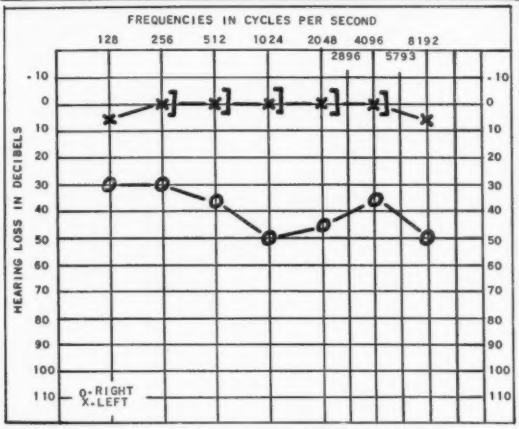
Résumé of Surgically Treated Cases

The last five patients whom we have treated surgically for congenital aural atresia were operated on in the manner described herein, by creating a tympanic membrane and a functional sound-conducting system. All five patients had unilateral atresia of the osseous type. One had an almost normal pinna, three had a moderate deformity of the auricle, and in one case the deformity was severe. In the first patient the indication for surgery was recurrent infection and a cholesteatoma in the distal portion of what appeared to be a blind-ending auricular fistula. In the second patient the plastic surgeon insisted on early reconstruction of the pinna. The third patient had had repeated episodes of tympanomastoiditis in both ears. In the fourth and fifth patients, an attempt had been made elsewhere to open the external auditory canal, but in each case the operation was not completed and subsequently the partially enlarged proximal portion of the future external auditory canal closed, and infection and a cholesteatoma developed.

In all five cases, a small middle ear space was found at operation. The tympanic membrane was replaced by a mass of solid, compact bone. Malleus and incus were characteristically displaced and more or less deformed in all cases; in one case, the malleus and incus were fused and the handle of the malleus was absent. In one patient the stapes had a rudimentary configuration. All patients had a normally functioning stapediovestibular articulation and a patent niche to the round window. In the first patient the facial nerve followed an

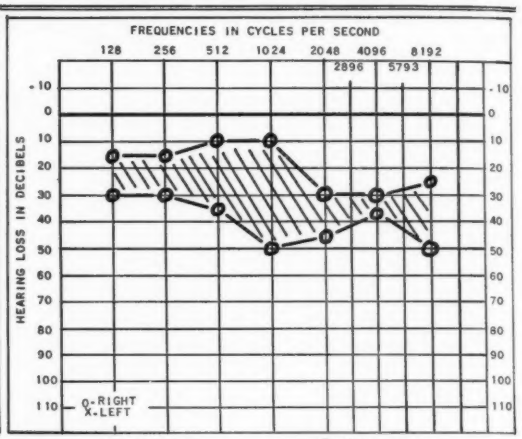
G. S., WF # 79 35 50

Age: 4 2/12 Pre-op.



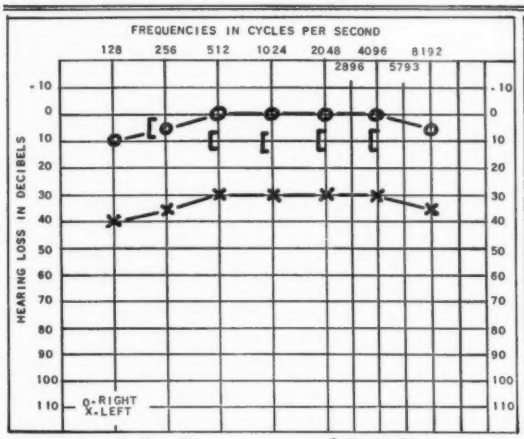
G. S., WF # 79 35 50

Age: 4 7/12 Post-op gain



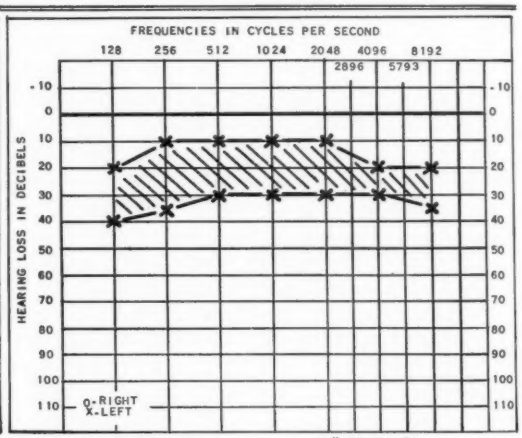
A. R., CM # 74 25 40

Age: 4 6/12 Pre-op.



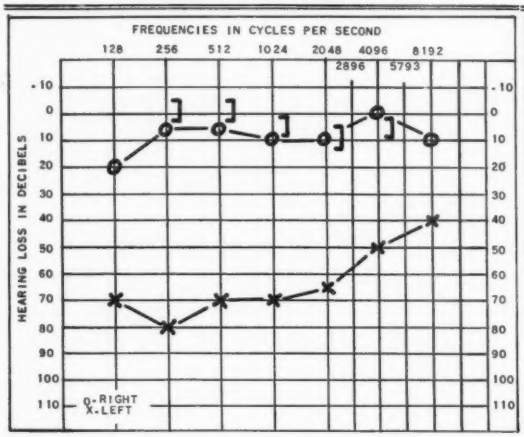
A. R., CM # 74 25 40

Age: 4 11/12 Post-op. gain



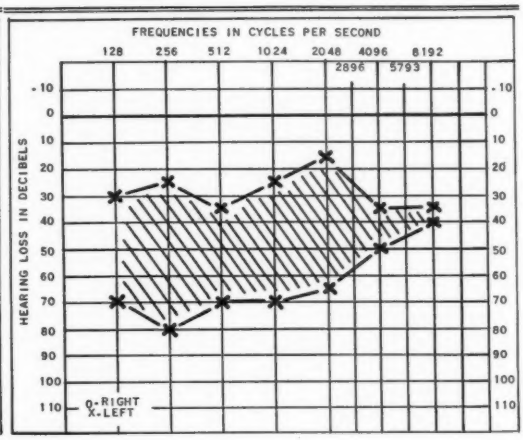
A. Z., CM # 81 93 82

Age: 10 7/12 Pre-op.



A. Z., CM # 81 93 82

Age: 11 Post-op. gain



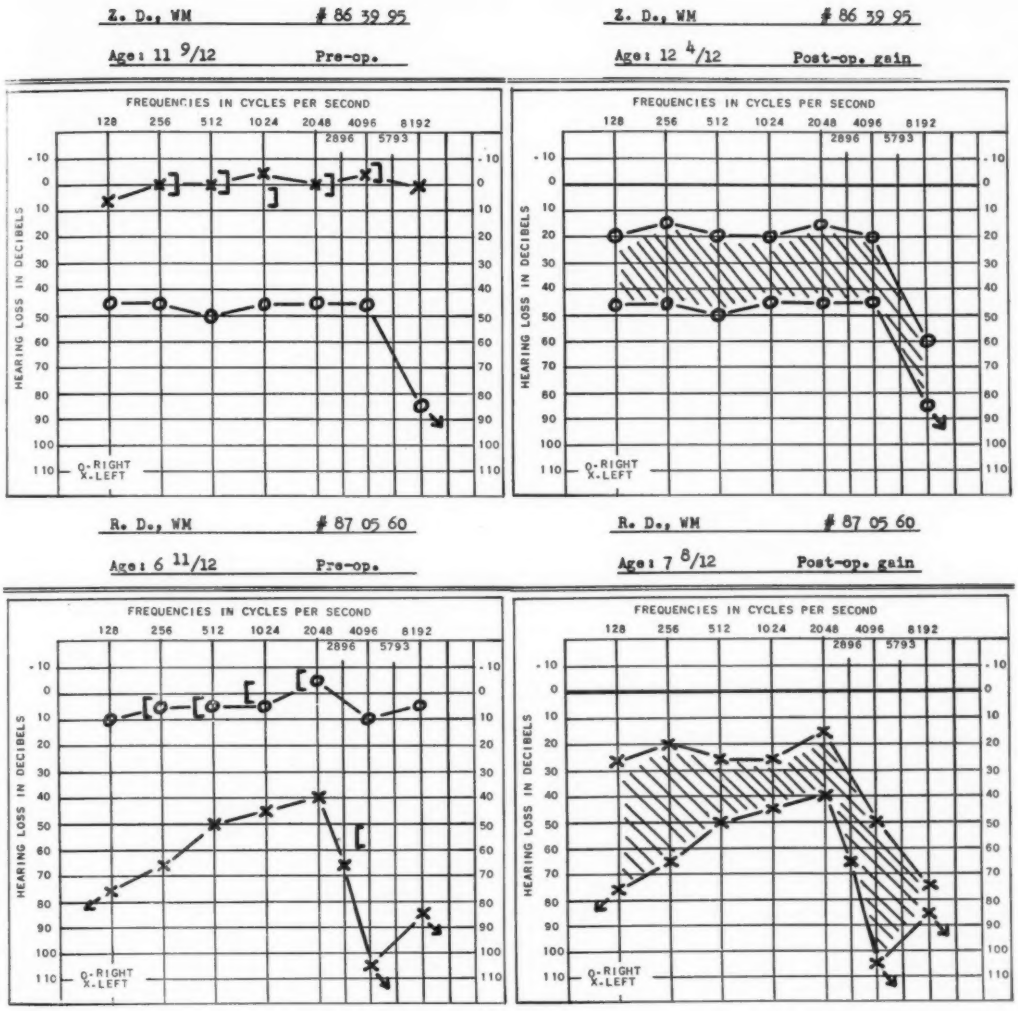

Z. D., WM # 86 39 95
Age: 11 9/12 Pre-op.
Z. D., WM # 86 39 95
Age: 12 4/12 Post-op. gain
R. D., WM # 87 05 60
Age: 6 11/12 Pre-op.
R. D., WM # 87 05 60
Age: 7 8/12 Post-op. gain
FREQUENCIES IN CYCLES PER SECOND
128 256 512 1024 2048 4096 8192
2896 5793
HEARING LOSS IN DECIBELS
-10 0 10 20 30 40 50 60 70 80 90 100 110
O-RIGHT
X-LEFT

FIGURE 8. Preoperative and postoperative audiograms of five consecutive patients in whom the technic described was used. Adequate masking was used in making the hearing tests.

abnormal course; the descending portion of the facial canal was in the area and at the level where one would expect the floor of the external auditory canal to be, and the stylomastoid foramen was on the anterior part of the lateral aspect of the mastoid process, immediately beneath the infraauricular fistulous canal. The preoperative and postoperative audiograms are shown in figure 8.

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The Electron and Proton, Signals for Biology

A PROSPECTUS FOR MEDICINE BASED ON ENERGY FLOW ACROSS A BALANCED SYSTEM OR TRANSDUCER, THE CELL; PREDICTION OF A CRUCIAL PHOTOCATALYTIC CHAIN

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Two principal themes are cited as bases for a systems analysis of biology: (1) The biologic organism is an energy transducer; (2) it can receive a signal input and transmit a signal output. The cell, being the central biologic unit, is an appropriate focal point for a biologic analysis. Study of a striated muscle-cell model provided considerable insight into the locus and mode of action of many hormones, vitamins, trace metals, and peroxidase-catalase units. It has been possible to interpret essential avenues for energy release and utilization. A direct outgrowth has been visualization of a proton pathway perhaps as important as the electron transport system. Several predictive aspects have arisen concerning the nature and operation of the "relaxing factor" of muscular activity.

A SCHEMATIC model which would unify our understanding of biologic cellular structure and function would be of immense utility to the field of medicine. Such a systems analysis could become the basis for more specific cataloguing of the many *intrinsic* diseases now grouped more or less nonspecifically as "metabolic," "functional," "systemic," "collagen-vascular" and "degenerative." *Extrinsic* diseases or injuries (traumatic, toxic, viral, radiative, etc.) also would be interpreted more lucidly in terms of their intrinsic effects. Improved methods of diagnosis and management would accrue.

The point might be illustrated by glancing quickly at a number of conditions which currently are considered to be unrelated but which may well have common roots. Would it not be productive if the physician could visualize the background that ties together essential hypertension, dysmenorrhea, bronchial asthma, glaucoma, peptic ulcer, otosclerosis, renal ischemic hypertension, scoliosis and Raynaud's

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JOHN C. LAMB

disease, to name but a few? Numerous experimental studies of the kinetic activity of muscle in our laboratory have culminated in the general observation that any agency which interferes with basic metabolism in muscle causes the muscle to remain contracted longer and conversely to require a longer time for relaxation. Fatigue, ischemia, decrease in temperature (cold), chemical catalytic poisoning, ionic changes, and hormonal deficiencies have been tested, and each has been found to induce a relatively contractured state in muscle as described above. It would appear, then, that a number of metabolic imbalances, interferences or deficiencies could produce a similar end result, namely, a tendency to a contractured muscle state. The trend in medicine has been to give "blocking" drugs or at times to perform extirpative surgery for conditions like those mentioned. Looking on these as contractured states wherein an internal potential energy input is required to achieve relaxation points rather more logically toward correction of some chemical deficiency or toward reparative surgery (as demonstrated in renal ischemic hypertension).

Basis of a Systems Analysis of Biology

How can we go about setting up this unifying model? Two principal themes might be cited as the bases for a systems analysis of biology. (1) The biologic organism is an energy transducer. (2) It can receive a signal input and transmit a signal output. The organism, organ system, organ, cell, and large, intermediate and small subcellular components all have their structural mass operationally arranged for conversion of energy from one form to another.

The cell represents the *central* biologic unit, and as such is an appropriate focal point for a biologic analysis. We have chosen the striated muscle cell for analysis because of its importance in the biologic organism and because much is known about it. Interpretation of other cell types can be made with appropriate allowances.

In regard to the two unifying themes, several important corollary principles, limitations and spheres of reference must be explicitly stated before such a sweeping simplification can be accepted as a basis for a model of a working cell.

Energy is manifest only in its interaction or containment in matter; even electromagnetic radiation and potential energy fields must have their origin and effect in matter interactions for us to know of their existence. This forces us to look at matter in *all* its various energetic interactions—chemical, mechanical and potential field. With this we can fit into their proper niches even those systems whose main function appears to be matter "pushing" or chemical synthesis of the matter that comes to function in the energy transducer mechanism.

It is important to recall that energy and mass are related in the universe in a broader sense and undergo conversion with a factor involving the square of the speed of light. On the other hand, it appears that biology is concerned with energy transduction at the optical electron-atomic kernel level without conversion of nuclear mass.

If we are basically concerned with the transducing of energy in biology, the First Law of Thermodynamics is invoked. This is a static bookkeeping system in which energy is transduced but conserved on an infinite time scale. A paradox is immediately introduced, however, since biologic energy transductions must take place in a finite time in order to accomplish the work function of cellular life. Therefore, a kinetic analysis or dynamic bookkeeping system must also be allowed.

Realization that a biologic unit must be built to minimize its entropy or probability of

dissolution but at the same time perform a work function or functions leads to a very important viewpoint based on the Second Law of Thermodynamics, in which the concepts of entropy and free energy are fundamental.

Stating that the biologic system is an orientation of chemical mass into a control and power system wherein energy is transduced leads at once to the question: What is the basic unit which carries the energy? We believe that the evidence is vastly in favor of this being the electron.

The background on which the chemistry of biology is enacted is oxidation-reduction and acid-base catalysis in which the electron and proton play the key roles. Hydrogen is the prime source of the electrons and protons, and oxygen is the prime acceptor of the electrons and protons. The primary chemical energy source for animal biology is the over-all hydrogen-oxygen couple.

To avoid having this primary energy-generating system dangle loosely among the various biologic cellular systems, we have envisioned a cyclic electron and proton circuit which couples the other systems in reaction with it. In order to account for the energy flow through the whole cellular mass, a set of impedance matchings like the meshings of gears must be acknowledged, for the electron is a relatively small mass with high energy which must motivate systems of relatively high mass and low energy.

Description of a system as a transducer capable of handling input and output signals implies a one-to-one input-output ratio. The implication is that the same number of electrons must leave as enter. This also complements electric circuit theory wherein the same number of electrons must return to as leave from a point in the circuit. This permits a view of biology situated on an open external circuit (closed elsewhere) while having a closed internal circuit.

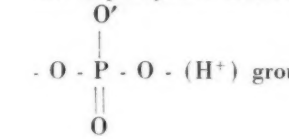
To summarize, the animal cell receives chemical mass of high free energy, operates with it reversibly, hence cyclically, carries out its work functions, repairs its entropy losses, and subsequently discharges a low free-energy chemical mass. The importance of this internally closed, cyclic, yet externally open free-energy flow process cannot be overemphasized. It enables the cell to be pictured as a *critically* damped oscillator receiving energy from the outside to overcome its internal and external damping associated with entropy changes and work functions. This permits much more straightforward orientation and analysis of its structure and activity.

A cardinal concept that has emerged is that biology is concerned with the handling of water and the components of water in many different sets. Some of the sets which are involved are the sets of separate water molecules, sets of electrostatically structured water dipoles, electron-proton-oxygen or hydrogen-oxygen oxidation-reduction sets, H_2O-HO_2-H_2O_2-OH-O_2 (and vice versa) paramagnetic free radical sets, simple OH^--H^+ acid-base electrostatic or ionic sets along with other sets at the hydronium level and beyond, hydrate sets connected with smaller to larger charged masses, viscous damping sets, hydrolytic sets, excited-state energy-quenching sets, hydrogen-bonding sets, dielectric sets, sets of liquid solvent molecules, oxidation-reduction or acid-base sets admixed with other electrode and electrolyte systems, especially those containing carbon, sulfur, the halogens, nitrogen, phosphorus, the first two alkali metals, sodium and potassium, the first two alkaline earth metals, magnesium and calcium, and a few of the transitional metals of the first and second series, iron, manganese, cobalt, molybdenum, along with zinc and copper. In addition, a most important aspect is the *quantized* nature of this "water" handling as a signal input-signal output process.

Perplexing Biochemical Questions

The most perplexing questions that face biochemists are as follows. What is the function of the electron transport chain? What happens to the protons or their equivalent if hydrogen, composed of electrons and protons, is the source of electrons for the electron carrier chain? What happens to the OH^- groups which are transferred in reverse to the electron flow in the carrier chain? How does the carbon electrode accompanying the basic sub-

strate, glucose, mix with the hydrogen-oxygen system; that is, what happens to the oxygen in the substrate bonded with carbon and hydrogen and where does the oxygen come from when the substrate carbon eventually leaves as carbon dioxide? How does the energy from the electron-carrier generating system actually transfer to drive the machinery for work in the cell? If there is a phosphorylative link at this juncture wherein $HO\text{-}PO''_3$ ions and adenosine diphosphate molecules with a terminal



group join as adenosine

where did the OH^- (and at times the additional H^+) or water go which was chemically bound between them? And so much of it! What happens to the other 350,000 calories of the 686,000 calories of free energy of combustion of a mole of glucose, if the phosphorylative energy-trapping mechanism at 40 moles of ATP x 8400 calories per mole of ATP produced captures only 336,000 calories in terms of chemical bonding? Is this remaining 350,000 calories radiated as heat or is some part used in regenerating the system? How is the system regulated and triggered so that it fits into a whole functioning cell with membrane activity, contractile activity, entropy-restoring activity, as well as metabolic respiratory activity? How do trace metals become vital to the system? Why are hormones and vitamins so important; what is their mechanism of activity, and how are they joined in a coordinated pattern of influence on cellular structure and function?

Mechanisms of Generation of Potential Energy Fields

Recognition that in biology there are electron and proton pressures which tend to create selective electric flow through conductive pathways and not through insulated spaces furnishes us with tangible mechanisms of potential energy field generation, including electrostatic, electromagnetic and paramagnetic fields. The concept of conductive pathways and insulators brings acknowledgment to the strategic *semiconductor* or *transistor* characteristics of carbon, the transitional metals, and other *doping* atoms found in biology. Among the several chief activities of lipids, unsaturated and saturated, and of proteins, unconjugated and conjugated, not the least are their special conductor and dielectric functions.

Prediction of a Photocatalytic Chain

Appreciation that both proton and electron electric flow, as well as oxygen transport in its various electron and proton states, must be accomplished points up both the crucial and elegant capabilities in this regard of metastable semiquinone intermediates and transitional metal chelates in coordination complexes. These chemical forms alternate through varying charged and paramagnetic states as they undergo cyclic oxidation reduction in a carrier chain activity which permits electric flow under potential energy gradients. These electrostatic and paramagnetic fields can be viewed as assisting in holding the components of the chain together, reducing activation energies, and opening the path for the simultaneous positive and negative electric flow and several kinds of oxygen flow involved in energy transduction. These simultaneous chains of flow can be pictured as combining (1) a paramagnetic oxygen-hydrogen free radical flow and (2) an electrostatic hydroxyl-hydrogen ion flow between the alternating paramagnetic and electrostatic oxidation-reduction pyridine and flavin nucleotide-cytochrome system which requires trace metals and vitamins and in all likelihood is hormone-moderated.

The accomplishment of this photocatalytic chain would be to utilize orienting potential energy fields to permit conduction and to couple internal respiration with oxidation-phosphorylation and deamination, sulfonation and deiodination, iron hydroxylation, and decarboxylation. The latter would be reversed during the reductive phase of internal respira-

tion. Interspersed with these respiratory cycles are reciprocating cycles going on in the contractile and relaxation mechanism and the DNA-RNA system of the muscle cell. The net result of the chemical transactions pushed by this electric flow is that an entropic model comprised of chemical mass manifesting various potential field interrelations is reoriented under free energy impress, thus affording the chance for subsequent decay with transfer of potential free energy in a special way to the environment. This restores the system for another cycle and does work in the process.

The photocatalytic chain would offer the link between the oxidation-reduction and acid-base activities of the energy-generating, work-performing, and control systems and provide answers for many of the perplexing questions posed earlier. This, of course, implies excited electronic states and highly developed mechanisms for prolonging and quenching of such states in the course of energy transmission and transduction. It brings into bold relief the role of electron delocalization among the π-electrons of the many biologic hydrocarbon ring structures, the metal chelates and coordination complexes, and many other components. It implies charge transfer and resonant coupling of spectral frequencies during energy flow. All at once a huge number of kinetic patterns and combinations of patterns in a random process become meaningful.

The quadrivalent character of a biologically ubiquitous and widely reactive carbon atom, in which an electron cannot be easily removed but in which in actuality electron removal, short-lived as it may be, must be accepted as occurring, provides par excellence the semiconductor and "indifferent" electrode for mediation of electron and proton transactions.

Biologic Interpretation of Periodic Table of Elements

The relation of electronegativity and electron affinity of the various elements of the periodic table to their ionic or covalent bonding characteristics, together with the ascending and descending orders of electronegativity and electron affinity among the elements, lends itself to a balanced system which pivots about the intermediate character of carbon. Given such an internal electrode system with capability for balance, given water for an electrolyte medium, and given the physical conditions existing on earth, it is not difficult to conceive of overlaying on this transducer a high free-energy mass input in the form of the electron-proton releasing agent, hydrogen, and electron-proton accepting agent, oxygen, and witnessing a low free-energy mass output in the form of water. In order to keep the electric circuit closed, the semiconductor, carbon, must also make the journey and be balanced by appropriate amounts of bound electrons, protons, carbon and oxygen in the input and output mass. Whatever irreversible entropy losses occur which become translated as internal mass loss must also be made up in input. These are a few brief comments concerning an extensive biologic interpretation of the periodic table of elements which has been carried out in connection with our effort to get an over-all look at biology.

The spectrum of electromagnetic radiations also has been carefully considered from a biologic view, since we are directly concerned with energy transfer. The central position in the electromagnetic radiation spectrum of visible light and near infrared and ultraviolet and the importance of such radiations to biology again are impressive. There is no need to recall that plant biology looks to radiant energy for its primary energy input or that some animal life can radiate light. The hidden implication is that we have quantized electromagnetic radiation inputs and outputs across both plant and animal biology and that biology offers a physicochemical mechanism for quantized transduction of these energy signals in the form of chemical mass and potential energy field phenomena.

Insight Gained From Study of Striated Muscle-Cell Model

In working with our striated muscle-cell model it has been possible to gain considerable insight into the locus and mode of action of many of the hormones, especially thyroxin, triiodothyronine, serotonin, epinephrine and norepinephrine, the fat-soluble and water-

soluble vitamins, trace metals, and peroxidase-catalase units, such that we would predict, as intimated, their role in a photocatalytic energy-transducing mechanism which involves electric flow and free radical formulation and moderation. It has been possible to outline pathways in which amination and deamination, sulfonation and desulfonation, iodination and deiodination, methylation and demethylation, carboxylation and decarboxylation, etc. are interpretable as essential avenues for energy release and utilization, just as phosphorylation and dephosphorylation have been recognized to be.

A direct outgrowth of the systems analysis has been the visualization of a proton pathway of perhaps equal importance to the currently recognized electron transport system. Interpretation of the purposes of and integration of the mechanisms of one-electron, two-electron, and four-electron flow patterns have become clarified. Several predictive aspects have arisen concerning the nature and operation of the so-called relaxing factor of muscle activity. Such a factor may be required in other basic work functions in biology, including nerve impulse transmission, chemical enzyme or hormone secretion, urine excretion, antibody elaboration, gastrointestinal absorption, bone formation, pulmonary oxygen absorption, carbon dioxide release, blood clotting, etc. This same type of factor may be reasonably predicted to be involved in plant biology in the process of photosynthesis.

Encouraging progress has been made in correlating the mechanical contractile-relaxation mechanism in muscle with metabolic chemical events, transmembrane electric events, and microstructure as exhibited by electron microscopy. The atomic logistics of the cell have become approachable. A mathematical formulation of the cell has come into reach. Answers to what would seem to be incidental or philosophical questions have appeared and shown themselves to be of profound importance. For example, why is intracellular pH buffered at about 7.4, temperature stabilized at about 37° C. in the working cell, resting transmembrane potential poised at 80 to 100 millivolts, electron pressure poised near zero on the potential scale? All these factors—pH, temperature, pressure, potential—are intensity factors which go along with corresponding capacity factors in the various energy functions of biology. We would suggest that their near midposition but slight displacement attests to the damped oscillative activity of energy transduction or flow as the main theme of biology.

We are well aware of the pitfalls inherent in an undertaking of this magnitude. We have been so impressed by its need and encouraged by its correlative and predictive value that we feel warranted at this time in stating this brief prospectus to the members of the medical profession. A detailed account of this work will be forthcoming.

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THE WIDENING SURGICAL FRONTIER

GERIATRIC surgery is now a reality. Physicians in all centers are aware of the increasing number of elderly patients seeking medical and surgical treatment. The rapid rise in the number of publications concerned with geriatric problems attests to the growing importance of this facet of medicine.

Zifferen has pointed out that since the first part of the twentieth century the number of persons 65 years of age and older has quadrupled, whereas the general population has only doubled. This seems to indicate that medical science has made some substantial gains in the prolongation of life beyond the age of 65 years. Yet, even though more people reach the age of 80 years, life expectancy beyond the eighth decade of life has not changed appreciably over the years. In 1900 the life expectancy at the age of 80 years was 5.1 years, and in 1953 it was 5.4 years. It would therefore appear that treatment of disease in the older segments of our population has benefited chiefly persons in the 65 through 80 year age group.

Today we are again at a widening frontier, for our concern now is with the patient beyond the eightieth year of life. In the past, surgical practice was rarely extended beyond the barriers commonly thought to be imposed by old age. All too frequently the octogenarian, nonagenarian or centenarian has been denied the benefit offered by even the most refined operative technics, and surgically correctable lesions have been allowed to progress to an irreversible state.

In a five and one-half year period from 1955 to 1960, 207 patients more than 80 years of age were operated on at the Baltimore City Hospitals. The number of operations totaled 284 and included general surgical, orthopedic, urologic, ophthalmologic and neurosurgical procedures. The experience gained from the treatment of these patients, in a hospital in which principally indigent persons are cared for, substantiates certain basic impressions. Many of the patients were brought to the hos-

ROBERT J. WILDER

RONALD H. FISHBEIN

pital in severe states of neglect, suffering from malnutrition and dehydration, and were without family or friends. An overwhelming proportion of the patients had multiple coexistent diseases unrelated to the primary surgical conditions. Frequently the concurrent illnesses were of such a nature as to affect the prognosis for life even more unfavorably than did the surgical illness.

Seventy-nine per cent of the patients had a preoperative diagnosis of heart disease. Fifty-seven per cent bore the preoperative diagnosis of pulmonary emphysema. Other respiratory problems included recent or resolving bronchopneumonia, active or inactive tuberculosis, and chronic tracheobronchitis. Additional operative risks were presented by large groups of patients exhibiting chronic renal impairment or cerebrovascular insufficiency. That these concurrent illnesses are deterrents to operation is true; that they preclude operation is false. Although 79 per cent of the patients had a preoperative diagnosis of heart disease, the postoperative complication observed most frequently was bronchopneumonia and the cause of death was most commonly related to the respiratory tract (30 per cent). Of the 69 patients who succumbed following operation, myocardial infarction was proved in only one case and cardiac irregularities played only a minor role in the mortality figures. This is further evidence that aged persons should not be denied the benefits of surgery because of their age or preoperative condition.

The preoperative preparation of the chronically ill, debilitated, aged patient is most important, and is influenced at the outset by the urgency of the operation. Surgical conditions requiring immediate definitive treatment limit the time available to correct any but the most glaring deficiencies. When the procedure is elective or when adequate temporizing measures are available in emergency situations, there is time for more careful correction of blood volume, nutritional deficiencies, metabolic and endocrine derangements, inflammations, and anemias. Preoperative preparation must be carried out with painstaking attention to all details. Base-line evaluations of cardiac status, pulmonary reserve, renal function and neurologic status are important in the preoperative appraisal of the elderly patient. All concurrent disease should be treated. An optimal anesthetic agent must be selected that will allow for adequate ventilation, insure the maintenance of preoperative blood pressure, and not interfere with cardiac rhythm. Regional block anesthesia and local anesthesia are useful in poor-risk cases. The time required to perform the operation is important, although there is no substitute for careful, deliberate, gentle handling of tissues and a smooth surgical procedure. Only in newborn infants is the need for gentle surgical technic as great.

In aged persons there seems to be a particularly delicate balance between life and death. The importance of a smooth postoperative course cannot be overemphasized. This is well borne out by the 62.5 per cent mortality rate among the patients who had postoperative complications and the 13.4 per cent mortality rate among those with apparently smooth postoperative courses. We are all too familiar with the sequence of events that leads from a rather uneventful operation to a wound infection, bed rest and soaks, atelectasis, pneumonitis, more bed rest, disappointment and depression, inadequate oral intake, supplementation of diet, decubitus ulcers and, finally, death from pulmonary emboli, cerebrovascular accidents or pulmonary or renal disease. The older patient cannot tolerate such postoperative complications. Restoration of blood volume, proper administration of fluids, careful tracheal toilet, and the resump-

tion of activity cannot be overemphasized.

The creation of an inviting, friendly, helpful hospital atmosphere is also a prime need among aged surgical patients, many of whom are completely alone. Numerous geriatric rehabilitation programs are springing up throughout the United States, with increasing participation of local, state and federal organizations. Although younger patients may be dismissed early in the postoperative period, this is not true in geriatric surgical practice. It should be the responsibility of the surgeon and all physicians concerned to continue their care until the patient not only is cured of his physical illness but also has returned to a place in society. Outstanding senior citizens have demonstrated continually that longevity is not a deterrent to continued achievement and enjoyment of life. Geriatric centers throughout the country have proved that rehabilitation of very old persons is almost always possible if there are interested persons to light the way and provide the proper atmosphere for them.

The over-all mortality rate among patients more than 80 years of age undergoing major operation is without question high, ranging from 15.1 per cent to 30 per cent in published reports. The divergence in the various studies may be explained by the different geographical, economic and racial backgrounds of the patients comprising the series and also by the varying definitions of mortality. In some series a surgical death is "one which follows operation, regardless of cause or time between operation and death, provided the patient is still in the hospital." Others define a surgical death as the death of "any patient who did not leave the hospital alive." In some reports, mortality is not defined at all. The Joint Committee on Accreditation of Hospitals bases the postoperative death rate on the number of deaths within 10 days of operation. It seems obvious that we should unify the definition of mortality in all such studies. Among aged persons, whose life expectancy is short, an evaluation of the over-all results of operation is most important and mortality figures based on a short postoperative course are not acceptable. The effects of anesthesia, prolonged bed rest, and the trauma of even the most gentle surgical procedure linger far longer in aged persons than one would like to believe. The succession of postoperative complications that may result in a fatal outcome is well known. Patients more than 80 years old may continue a downhill postoperative course for six months or more before death intervenes. A mortality rate based on death 30, 60 or even 180 days following operation, therefore, would not give a true picture of immediate postoperative mortality but would allow a clearer evaluation of the results of operative procedures in patients whose life expectancy is relatively brief. It would give an indication of the over-all effect of the disease process as well as of the operation performed.

In our series the mortality rate is 33.3 per cent based on deaths occurring within 30 days after the operative procedure, or as long as 50 days postoperatively if the patient was doing poorly at the end of 30 days. If we extend the mortality figure to include deaths within six months of operation, however, the rate rises to 42.9 per cent. Despite the high mortality rate, the risks of geriatric surgery seem justified when a man who had a pin inserted in the left hip at the age of 90 years and a pin inserted in the right hip at 93 returns to the outpatient clinic at the age of 96 years for treatment of a skin rash; or when an 80 year old man survives not only the closure of a duodenal ulcer but also a subtotal resection necessitated by leakage from a second ulcer 12 days later; or when an 89 year old patient returns to work after resection of a massive abdominal aneurysm. There is little doubt that the over-all surgical mortality rate for patients beyond the eighth decade of life is high. However, the majority of these surgical procedures are not elective, and the excellent results achieved in many of these acutely ill patients encourage us to go on. In fact, postponement of elective procedures in aged persons with or without significant concomitant disease is unwise, since the operative risk is many times greater when a benign operative condition is allowed to progress to an emergency state.

Elderly patients show a remarkable capacity to tolerate major operations provided the postoperative course is smooth and without complications. We should not hesitate to offer surgical procedures to those beyond the age of 80 years. Instead, we should continue to improve all facets of preoperative and postoperative care, anesthetic agents, surgical skills, and rehabilitation units so that the widening frontier may ever extend. For who can say what the upper limit of life may be?

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THE DANGERS OF DIAGNOSTIC X-RAY EXPOSURE

RUSSELL H. MORGAN

In recent years the biologic effects of small doses of ionizing radiation, such as those used in diagnostic medical practice, have been the subject of considerable discussion in the scientific and the lay press. It has been pointed out that these effects are of two general types, genetic and somatic. The genetic effects are caused by irradiation of the reproductive organs and lead to the appearance of mutations in succeeding generations. They appear to be irreversible, and hence small doses of radiation delivered over a period of time are cumulative in the damage they may create. Also, the effects appear to be proportional to the dose of radiation and thus are more severe when the accumulated dose is large than when it is small.

The somatic effects are caused by irradiation of certain critical organs and may lead, after a variable number of years, to a number of neoplastic states, including leukemia, skin cancer and bone cancer. In general the effects are greater when the dose of radiation is large than when it is small, but it is not at all certain that the magnitude of the somatic damage is entirely proportional to the dose of radiation. It is possible that very small doses may create little or no damage, i.e., that there may be a threshold dose below which no somatic effects may be expected. However, because the scientific data on this point are so uncertain, prudence dictates that in the development of protective measures against radiation one must assume that a somatic threshold dose does not exist, until conclusive evidence to the contrary is forthcoming.

That exposure to ionizing radiation may have deleterious effects was recognized early in this century, soon after the discovery of the x-ray. Physicians who used x-rays in their practice found it convenient to test their fluoroscopic equipment each day by observing how well they were able to see their hands when they placed them in the x-ray beam. After a number of years, changes developed in the skin of the hands of some of these men and ultimately these changes degenerated into cancer.

With the recognition that exposure to ionizing radiation may be hazardous, physicians began to take precautions against the delivery of any substantial amounts of unnecessary radiation both to themselves and to their patients. Leaded aprons and gloves were adopted as standard apparel for physicians during fluoroscopy. Radiographic technics were developed which reduced exposure of the patient to radiation, and greater attention was paid to a variety of factors that might reduce the dose of radiation to both the patient and the physician. In the 1920s, the Advisory Committee on X-ray and Radium Protection was formed by a number of outstanding radiologists and radiation physicists to make recommendations concerning the safe use of x-rays in medical practice. In the years since its founding, this quasi-official committee, now known as the National Committee on Radiation Protection, has played an outstanding role in setting forth criteria for the application of x-rays and other sources of radiation in medicine with minimal exposure of patient and physician alike.

In spite of the history of the early radiation

workers and in spite of the excellent work by the National Committee on Radiation Protection, there has prevailed in the medical x-ray field a certain laxity or inconsistency in the manner in which radiation safety measures have been applied. The reasons are not difficult to find. In most medical schools, instruction on the safe use of fluoroscopic and radiographic equipment has been either nonexistent or woefully inadequate. Since most of the x-ray apparatus in this country are used by physicians who have not had postgraduate radiologic training, such apparatus are often operated without regard for the protective standards recommended by the N.C.R.P. Also, not all residency programs in radiology have provided satisfactory training in the safety aspects of the diagnostic branches of the science. Radiation doses for diagnostic purposes are much smaller than those delivered in radiation therapy and hence there has been a tendency to overlook safe operating practices in this field.

The laxity in the application of protective measures against radiation in medical practice has led some public authorities to suggest regulation or sharp curtailment of the medical use of x-rays. To evaluate the wisdom of these suggestions, let us examine the available data on the quantitative relationships between radiation dose and biologic damage, both genetic and somatic, and the available data on the doses received by persons undergoing x-ray examination. Although entirely satisfactory information in both these categories is not at hand, sufficient data are available to give a general indication of the biologic damage that may be expected in the general population from medical x-ray exposure.

In the field of genetics, it appears that a radiation dose of 30 to 50 r to the reproductive organs is needed to double the spontaneous mutation rate of the population. Since this spontaneous rate is approximately 2 per cent, it follows that if the population at large, previous to and during its reproductive life, receives a gonadal dose of from 30 to 50 r, the number of mutations appearing in the population may be expected to approach 4 per cent of all live births. The foregoing statistics also apply to individuals. If a patient receives a gonadal dose of 30 to 50 r prior to the creation of his or her family, the probability of a mutation in any one of his or her children is increased from 2 per cent to 4 per cent.

Now, the chances that a person would receive a gonadal dose of more than a small fraction of 30 r during his lifetime are rather small, if proper technics are employed in fluoroscopy and radiography. This is particularly true if the direct radiation from the x-ray tube is prevented from falling on the reproductive organs, for, if this is done, the gonads are exposed only to the very small amounts of radiation scattered from the tissues that are irradiated directly. The difficulty here, however, is in the consistent use of proper fluoroscopic and radiographic technics. Physicians customarily leave the performance of radiographic exposures to their technicians, and supervision of their methods usually is only cursory at best. Also, in fluoroscopy, physicians frequently are tempted, because of overextended schedules, to reduce the time taken for dark adaptation and to compensate for this by using increased x-ray tube currents and consequently higher radiation dose rates. As a result, the gonadal dose received by the population from medical x-rays is considerable greater than it need be, and in the United States this dose has been estimated to be about 5 r for an average person prior to reproduction. Although such a dose may not double the mutation rate, its genetic effects are sufficiently great that geneticists have expressed concern regarding it. All radiation-induced mutations are likely to be deleterious and hence will cause a burden on society. Also, the use of medical x-rays is increasing and the burden therefore is likely to become greater. There can be little question that efforts should be instituted to reduce the gonadal radiation dose received by the population.

In the realm of somatic damage, quantitative data on the relationship between radiation dose and biologic effect are quite meager in the ranges of dosage employed in x-ray diagnosis. Some British studies suggest that a whole-body dose of a few roentgens received by a fetus during pelvimetric or fetometric

x-ray examination of the mother may double the spontaneous rate of leukemogenesis during the first 10 years of life. A study of the incidence of leukemia among the survivors of the atomic explosions in Japan suggests that the probability that leukemia will develop following whole-body exposure is 1 to 2 parts per million for each roentgen of whole-body exposure a person receives and for each year he survives after exposure. As interesting as these Japanese data may be, their application to diagnostic x-ray problems is extremely hazardous. When proper technics are used in fluoroscopy and radiography, only a small part of the body is exposed, in contrast to the whole-body exposures of the Japanese. Further, although relatively reliable data on the surface doses received by persons during radiographic exposure are available, these doses become very nonuniform in terms of depth, and calculations of the doses received by an irregularly distributed hematopoietic system are therefore almost impossible. Fortunately, except possibly for the British data, no clear evidence has developed to indicate that diagnostic x-ray procedures are producing substantial amounts of somatic damage in the population. Hence, the absence of good quantitative data on these effects perhaps is not of great concern. This is not to say that these effects are insignificant, of course. Indeed, since radiation is known to produce important somatic damage when larger doses are delivered, prudence requires that the doses applied in x-ray diagnosis be kept as small as possible, in accordance with good clinical judgment.

With the foregoing discussion in mind, let us return to the question, Should diagnostic x-ray practice be regulated or sharply curtailed? At present there does not appear to be sufficient evidence to justify any substantial limitation in the use of diagnostic x-rays. Although the gonadal dose received by the population from such examinations is appreciable, there is reason to believe that application of improved fluoroscopic and radiographic technics might reduce this dose by a factor of 10 or more. Also, a program to curtail services implies a mechanism whereby the medical benefits of diagnostic x-rays can be evaluated in terms of their biologic risk. Since such an evaluation is almost impossible to make in most cases, it seems clear that the physician must remain free to determine when diagnostic x-rays are to be taken. This freedom, of course, in no way carries with it the freedom to apply x-rays unsafely. Indeed, the use of improper operating procedures under any circumstances can only be condemned. Therefore it may be expected in the years ahead that increasing efforts will be made by health officials and other members of the medical profession to institute whatever measures are necessary to overcome the current practice of many physicians who do not provide adequate protective measures against unnecessary x-ray exposure.

It may be anticipated that all medical x-ray equipment will come under the continual surveillance of health authorities whose responsibility it will be to ascertain as far as it is possible to do so that x-rays are applied to patients throughout this country with a high level of safety. The profession has a responsibility to cooperate maximally in this development. Medical benefit is likely to far outweigh radiation risk if x-rays are applied properly. On the other hand, one cannot be nearly as certain of this if safe operating practices are disregarded.

What are the principles which form the basis of safe radiographic and fluoroscopic technic? First, the dose of radiation in each case must be maintained at as low a level as possible. This requires that the x-ray apparatus be equipped with collimating cones that precisely limit the radiation to the anatomic structures to be examined. The collimating device should have a light beam which accurately defines the irradiated region, and if the field of examination includes the reproductive organs these structures should be shielded from the direct radiation which otherwise would fall on them from the x-ray tube. Ideally, the x-ray apparatus should be equipped with instrumentation that measures precisely the quantity of radiant energy delivered to the patient at each exposure. From such information one can quickly determine whether

or not the x-ray apparatus is operating properly and has been skillfully used by the technician. The x-ray beam should be filtered by aluminum at least 2 mm. thick to reduce the nonpenetrating components of the beam reaching the patient. Doses for chest films should average 0.05 r; for skull films, 0.5 to 1.0 r; for abdominal films, 0.5 to 2.0 r, and for lateral abdominal films 5 to 10 r at the surface of the patient. Before any equipment is used, checks should be made to determine if these safety criteria are met.

In fluoroscopy, proper technic calls for the use of small fields and short exposure times. The distance between the x-ray tube and the patient should be 18 in. or more, and the radiation dose rates should be less than 6 r per minute. Proper technic also calls for limitations in the use of fluoroscopy in children. Since these patients are small, any fluoroscopic examination is likely to involve a much larger proportion of the body than it would in an adult. Further, there is evidence that children's tissues are more sensitive to radiologic damage than adults' tissues. Finally, radiographic examination of children often will yield as much diagnostic information as fluoroscopy, or more. Since fluoroscopic examinations deliver substantially higher doses of radiation than radiographic examinations, fluoroscopic examination of children should generally be avoided.

It should be clear by this time that fluoroscopic and radiographic technics should be used in medicine only by physicians who are fully aware of their hazards and who are able to maintain safe operating conditions in their practice. The physician who plans to use x-rays should always remember that the freedom to use them without professional restriction carries with it the responsibility to protect his patients from all unnecessary radiation. If this responsibility is met, one can anticipate that the public's concern about radiation hazards in the medical field will disappear rapidly and the great benefits to be derived from medical x-rays will be maintained.

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THE LAST MILE

WARFIELD M. FIROR

FOR some doctors, medicine is merely a branch of biology, a scientific discipline in which a human being is just another species of animal. This point of view inevitably affects the physician's attitude toward his patients, particularly when a patient is afflicted with an incurable disease or is nearing the end of life. Regardless of one's philosophy, everyone will agree that one fact that differentiates human beings from lower species is our ability to record and to transmit knowledge. This ability influences a person's reaction to serious illness and to death. A second attribute of mankind is the possession of a highly developed imagination. This too plays a major role in man's reaction to fatal illness.

By way of illustration, one can contrast the reactions of a woman and a dog to carcinoma of the breast. Biologically this neoplasm is similar in both species. The disease begins as a painless hard lump which, if untreated, increases in size, ulcerates, discharges foul secretion, and eventually brings about the death of the host. The dog reacts only by licking the ulcerated area and by restricting its activities when weakness develops. The woman who discovers a lump in her breast immediately recalls many of the frightening articles she has read in magazines. Her partial knowledge evokes anxiety and sometimes frank terror. Her imagination is unleashed; she visualizes a large, deforming operation, huge hospital bills, the interruption of her immediate plans. She thinks of the added burden on an already overburdened family. She recalls her neighbor who died of painful metastases just two years after her breast had been removed. As her imagination runs unchecked, she thinks of dying just when her children need her most.

Every physician knows that all these consequences of a malignancy do occur. These are some of the concomitants of serious illness

human beings. They are actualities in our daily practice, and the purpose of this editorial is to urge all who read it to give critical consideration to their own way of helping the patient and the relatives when specific therapy fails. When this occurs, the physician can adopt one of three courses of action: (1) avoid the situation by referring the patient to the family doctor, (2) maintain an optimism that is full of cheerful but false prognostications, or (3) explain to the family the improbability of curing the patient and the necessity of directing all of one's efforts toward the alleviation of physical and mental suffering. More precisely, this means that it is just as much a physician's duty to help the patient to die comfortably when death is inevitable as it is his duty to prolong life while there is hope of recovery. The alleviation of physical suffering is relatively easy if the physician is not a fool. Unfortunately there are many physicians who refuse opiates to patients with incurable maladies because the patients might become addicted! What nonsense!

From experience I am convinced that another very important aspect in the handling of terminal illness is to advise against the use of treatments designed solely to prolong existence. Useless transfusions and forced feedings are unjustified. Occasionally this may require a firm stand on the part of the physician, but more frequently the needless postponement of death is the result of the physician's fear of criticism.

The alleviation of mental suffering is an altogether different matter and often demands the utmost patience, perception and sacrifice on the part of the physician. Just to walk along with the patient and family day after day, so that they do not feel deserted, is one of the finest ways to help. Paradoxical as it may sound, it is in helping patients to die comfortably that the ministry of healing can sometimes achieve its greatest height.

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To Our Subscribers:

We regret that limitations of space have made it necessary to omit some of our regular features this month. However, all of these features—the Scientific Exhibit, Nutrition in Clinical Medicine, Clinicopathologic Conference Report, Self-help Devices, Clinical Studies—and the full content of clinical articles will appear as usual in the June issue. That issue will also contain the third and final group of papers from the series on "Emergency surgery for the general practitioner."

THE EDITORS

Great Names in American Medical History

New Jersey

Henry Leber Coit, M.D.

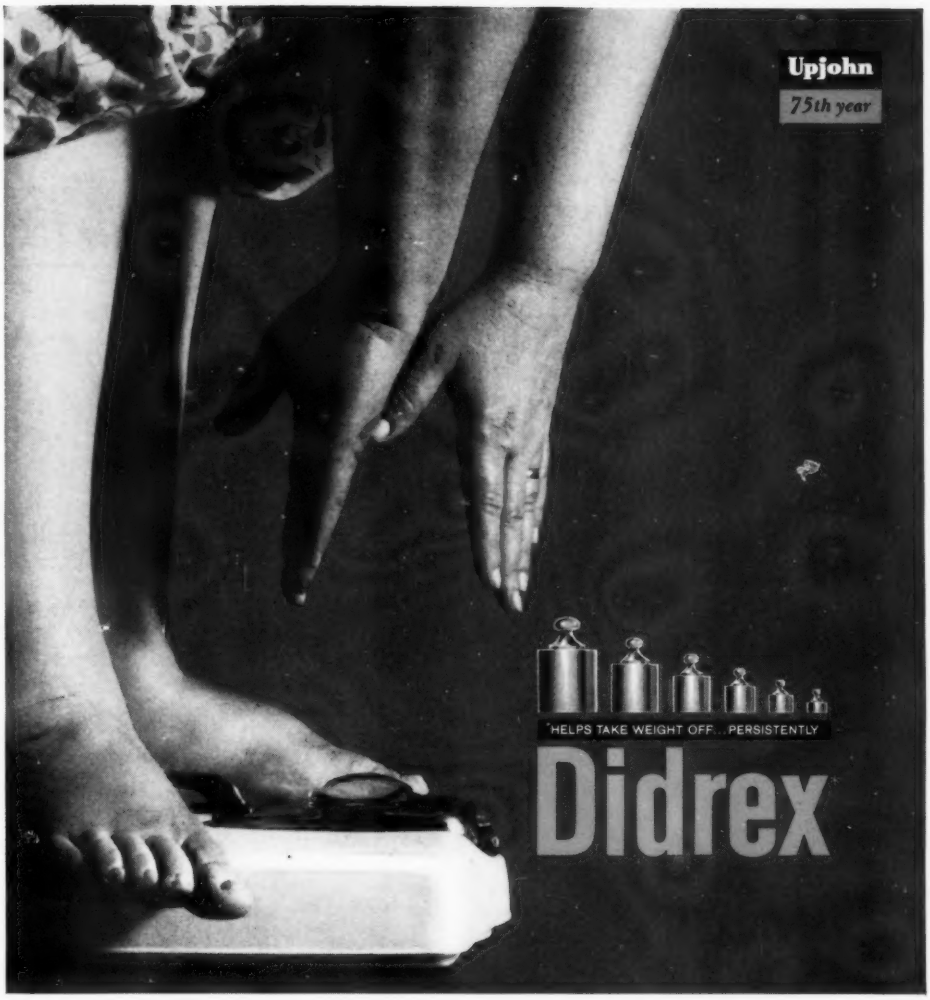
This is one of a series of biographic sketches of outstanding physicians of the past from each of the 50 states. The subjects have been selected by the medical society of each state or its designated committee.

AMONG the unsung names in the history of medicine is that of Henry Leber Coit (1854-1917) of New Jersey. He is credited, among other accomplishments, with being the originator of certified milk and the organizer of nationwide medical milk commissions. He was the founder and the first pediatrician of the Babies' Hospital, now known as the Coit Memorial Hospital, of Newark, New Jersey.

Dr. Coit was born in Peapack, New Jersey, on March 16, 1854; he was the son of a Methodist minister, who died when the boy was 12 years old. While getting his early education, he worked in a drugstore in Newark, sleeping under the counter at night. He was graduated from the New York College of Pharmacy in 1876 and served there as instructor while attending medical college. His M.D. degree was awarded by the Columbia University College of Physicians and Surgeons in 1883, and he served an internship and practiced as a general practitioner in Newark.

Dr. Coit's first son had diphtheria during an epidemic. While trying to get pure milk for his dying boy, he observed the filthy conditions at some of the farms near Newark, where the milk was dipped by hand from 40 qt. cans. This inspired him to a study of the milk supply. He tried to obtain legislation for the control of milk supplies but was unsuccessful. He then read a paper on December 5, 1892, before the Practitioners' Club of Newark. In this paper he presented his plan for chemical, bacteriologic and veterinary standards of milk production. He advocated that dairy hygiene and the health of dairy employees be supervised by physicians. From this came the phrase "certified milk." The first Medical Milk Commission was organized in Essex County, New Jersey, in 1893, and Dr. Coit was its first president. At his death on March 12, 1917, 60 commissions were functioning in the United States and Canada, with several others in Europe and Asia.

In 1910 Dr. Coit became the founder and first president of the New Jersey Pediatric Society. The Babies' Hospital of Newark was second only to the one which was founded in New York. In 1916 during the great epidemic of poliomyelitis, although he was 62 years old, Dr. Coit organized the Citizens Relief Committee, which provided funds for physical therapists and specially trained nurses for poliomyelitis patients.



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Supplied: 50 mg., benzphetamine hydrochloride, press-coated, scored tablets, in bottles of 100 and 500.

*Trademark—brand of benzphetamine hydrochloride, Upjohn.

References: 1. Stough, A. R.: Weight loss without diet worry: use of benzphetamine hydrochloride (Didrex). Journal of the Oklahoma State Medical Association, **53**:760-767 (November) 1960. 2. Oster, H., and Medlar, R.: A clinical pharmacologic study of benzphetamine (Didrex), a new appetite suppressant. Arizona Medicine, **17**:398-404 (July) 1960. 3. Simkin, B., and Wallace, L.: A controlled clinical trial of benzphetamine (Didrex). Current Therapeutic Research, **2**:33-38 (February) 1960.

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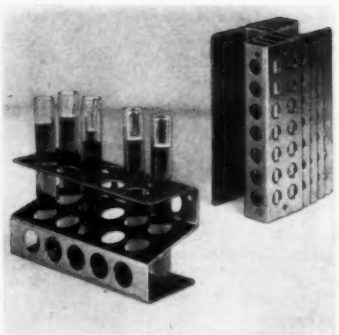

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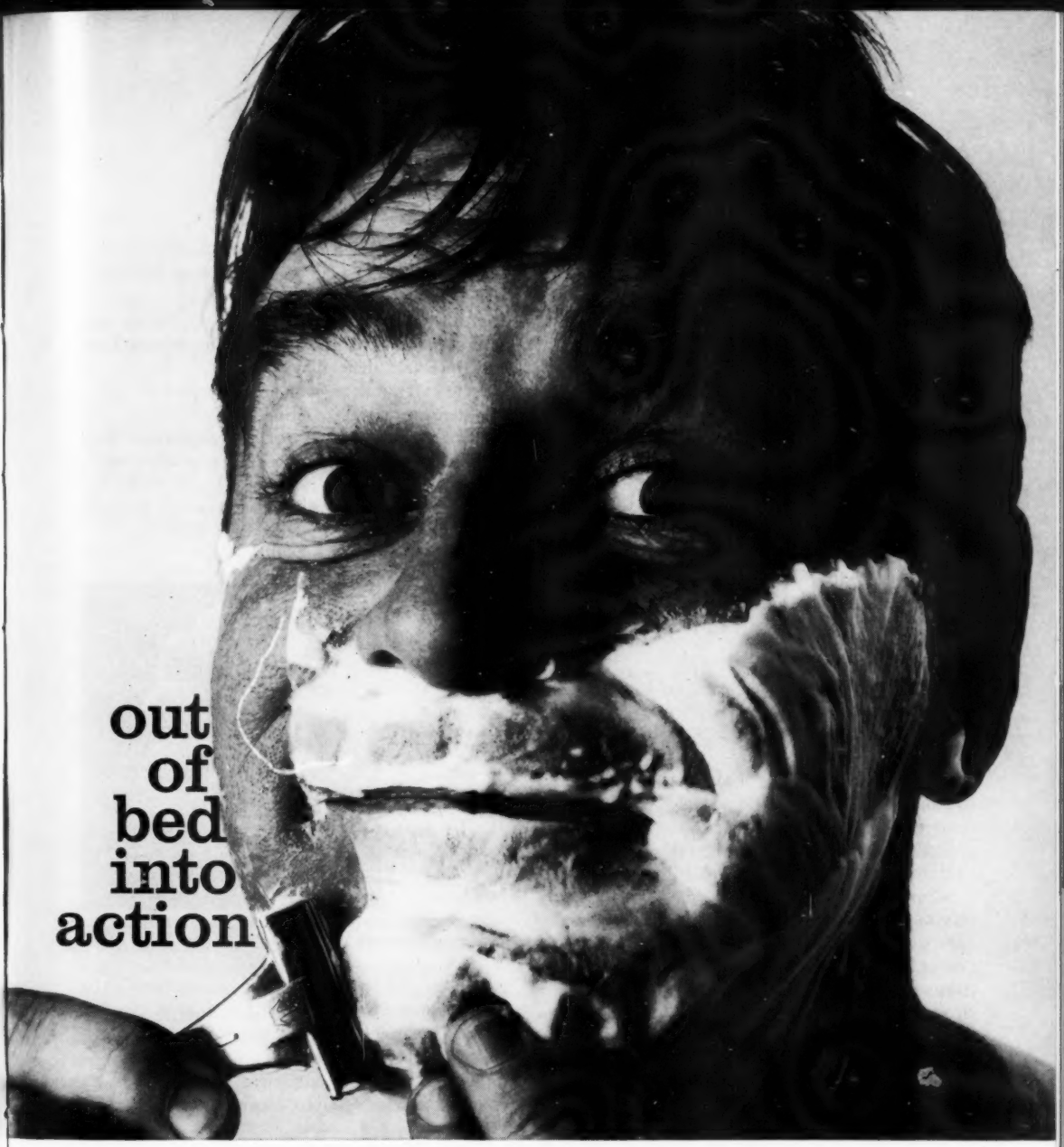
(Continued on page A-96)



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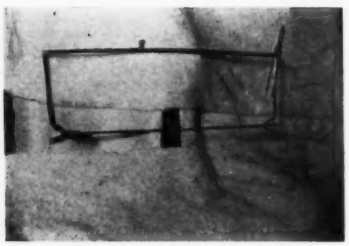


• YARINGTON RETRACTOR

DESCRIPTION: During any surgical procedure in which a small incision is used and wound exposure and hemostasis are desired, this instrument provides self-retaining, indirect traction. It allows constant traction on Allis clamps and hemostats placed on the wound edge, and provides opportunity for adjustment of the degree of traction and the addition of more clamps.
PRODUCER: Henry C. Betz Co., Philadelphia.

• CONVERZYME® LIQUID

PURPOSE: To treat nervous dyspepsia and functional digestive disorders.
COMPOSITION: Each teaspoonful contains:

Standardized proteolytic enzyme (papain)	10 mg.
Standardized amylolytic enzyme	80 mg.
Homatropine methylbromide	2.5 mg.
D-Sorbitol	4.4 gm.

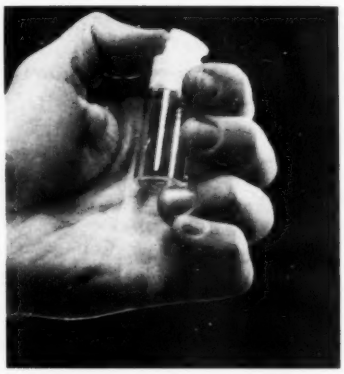
DOSAGE AND ADMINISTRATION: 1 or 2 teaspoonfuls with or after meals. If suggested dosage proves laxative, it should be adjusted to requirements of patient.
HOW SUPPLIED: 1 pt. bottles.
PRODUCER: B. F. Ascher & Company, Inc., Kansas City, Mo.

• LIDA-MANTLE-HC® AND NEO-LIDA-MANTLE-HC®

PURPOSE: Topical antiinflammatory and antipruritic therapy.
COMPOSITION: Lida-Mantle-HC contains lidocaine and hydrocortisone in the ACID MANTLE® vehicle. Neo-Lida-Mantle-HC contains neomycin in addition to the above ingredients.
INDICATIONS FOR USE: Itching and pain accompanied by inflammation. Neo-Lida-Mantle-HC is used in actual or threatened infection.
HOW SUPPLIED: ½ and 1 oz. containers.
PRODUCER: Dome Chemicals Inc., New York.

• ANTIVERT® SYRUP
(New Product Form)

PURPOSE: To treat vertigo.
COMPOSITION: Each teaspoonful (5 cc.) contains 25 mg. nicotinic acid and meclizine equivalent to 6.25 mg. meclizine hydrochloride.
INDICATIONS FOR USE: Ménière's syndrome and apprehension and mental confusion arising from nicotinic acid deficiency.
CAUTION: This drug is contraindicated in severe hypotension and hemorrhage.
DOSAGE AND ADMINISTRATION: 2 teaspoonfuls three times a day just before meals, or as directed.
HOW SUPPLIED: 1 pt. bottles.
PRODUCER: J. B. Roerig and Company, Division of Chas. Pfizer & Co., Inc., New York.



• OPTISEAL STOPPER VIAL

DESCRIPTION: Featuring a locked-on, one-piece polyethylene cover, this vial for liquids, powder or pills is unsealed by breaking off a protruding plastic knob. The knob then can be used as a stopper to reseal the opening.
PRODUCER: Kimble Glass Company, Toledo.

• VI-SYNERAL® ONE-CAPS
(New Dosage Form)

PURPOSE: Dietary supplement.
COMPOSITION: This product contains 10 vitamins and seven minerals.
DOSAGE AND ADMINISTRATION: 1 capsule daily with any meal.
HOW SUPPLIED: Bottles of 28 and 100 capsules.
PRODUCER: U. S. Vitamin & Pharmaceutical Corp., New York.

THE MEDICAL Bookman

► CLINICAL PSYCHIATRY

By W. Mayer-Gross, M.D., Senior Fellow, Department of Experimental Psychiatry, University of Birmingham Faculty of Medicine, Birmingham, Eliot Slater, M.D., Director, M. R. C. Psychiatric Genetics Research Unit, Institute of Psychiatry, London, and Martin Roth, M.D., Professor of Psychological Medicine, University of Durham Medical School, King's College, Newcastle-upon-Tyne, England. Ed. 2. 704 pages, illustrated. 1960, The Williams & Wilkins Company, Baltimore. $13.00.

The second edition of a British textbook of psychiatry that has been standard in England since it was first published in 1954, this book is devoted primarily to an organic and descriptive approach. The introductory chapters include material on the foundations and history of psychiatry as well as very short, superficial summaries of the various contemporary schools, including the Kraepelinian approach, psychobiology, psychoanalysis, Pavlovian psychiatry and existential analysis. The remainder of the book is organized into various subdivisions dealing with such things as mental deficiency, psychopathic personality, neurotic reactions, the affective psychoses, schizophrenia, epilepsies, brain afflictions and aging. The relatively complete discussion of child psychiatry is mainly of a descriptive nature. As is typical of most British textbooks of psychiatry, a rather thorough discussion of legal and administrative aspects of psychiatry is included in this volume.

It is surprising how little of the dynamic approach to psychopathology is present in this book. I doubt that this text has any advantages for the student or resident over such standard American texts as that of Noyes and Kolb. The latter book is preferable because it presents both a descriptive and dynamic approach to many of the conditions described. The British textbook might be recommended strictly as a reference book, but it should be emphasized that there are more valuable standard texts for the medical student and resident interested in psychiatry.

E. M. L.

► PHARMACOLOGY
The Nature, Action and Use of Drugs

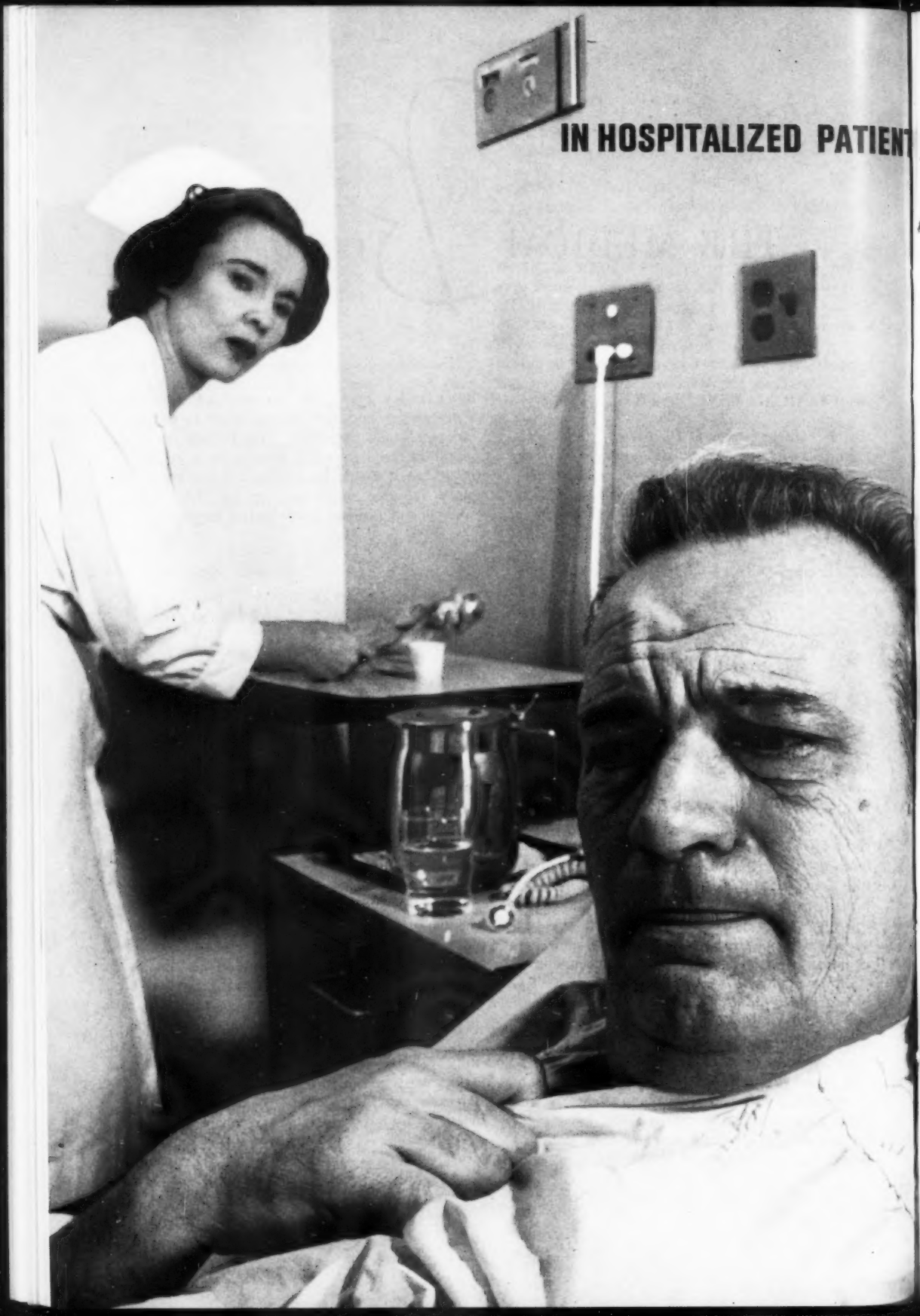
By Harry Beckman, M.D., Chairman, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry, Milwaukee. Ed. 2. 805 pages, illustrated. 1961, W. B. Saunders Company, Philadelphia and London. $15.50.

The first edition of this excellent text appeared in 1958. This revision serves both to bring the subject matter up to date and to improve readability and continuity by well-chosen rearrangements in organization of material.

The basic arrangement in three sections is retained. The first section remains an interesting philosophical introduction to the study of pharmacology. Section 2, presenting "Some pharmacologic background," has been expanded by discussions of the development, nomenclature and control of new drugs. In the third section, 68 chapters are devoted to the actions and uses of drugs, classified by principal pharmacologic activity. The organization of this section has been improved by the addition of new chapters on drugs used in diabetes mellitus and in atherosclerosis and the deletion of chapters on diagnostic aids and radioactive tracer elements.

F. T. M.

(Continued on page A-132)

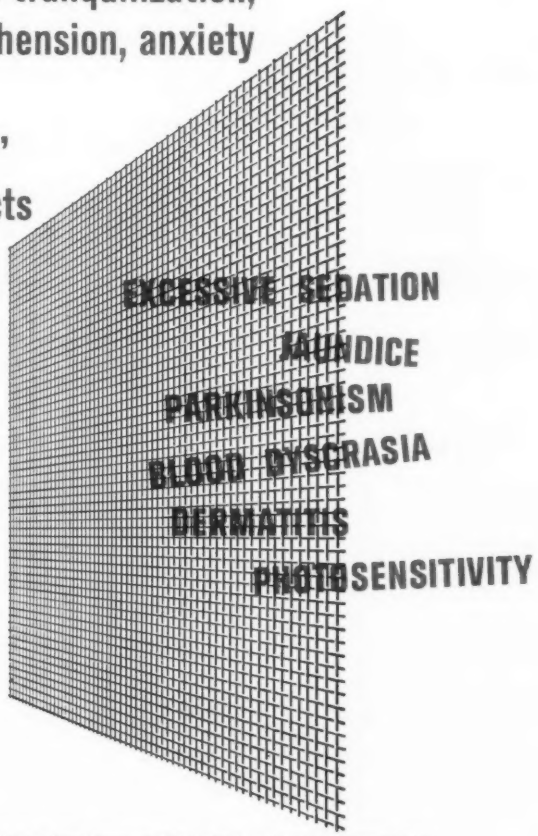

IN HOSPITALIZED PATIENT

Mellaril®

THIORIDAZINE HCl

provides highly effective tranquilization, relieves agitation, apprehension, anxiety

and "screens out" certain side effects of tranquilizers, making it virtually free of:



"The value of the phenothiazines as tranquilizers has been established. [However] many distressing side effects have been reported with these drugs.... Thioridazine [Mellaril] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines."[1]

In Agitated Medical/Surgical Patients—"A new phenothiazine derivative, thioridazine [Mellaril], was used to treat 71 patients, most of whom were unduly agitated and disturbed due to hospitalization for medical or surgical conditions.... The response to treatment was considered satisfactory in 83.4 per cent of patients.... In agreement with the published results of other investigators, we believe that thioridazine shows a greater specificity of tranquilizing action and freedom from serious toxic effects when compared with some of the other phenothiazines."[2]

Mellaril is indicated for varying degrees of agitation, apprehension, and anxiety in both ambulatory and hospitalized patients.

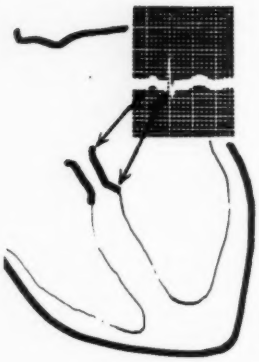
Usual starting dose: Non-psychotic patients – 10 or 25 mg. t.i.d.; Psychotic patients – 100 mg. t.i.d.

Dosage must be individually adjusted until optimal response. Maximum recommended dosage: 800 mg. daily. Supply: Mellaril Tablets, 10 mg., 25 mg., 50 mg., 100 mg.

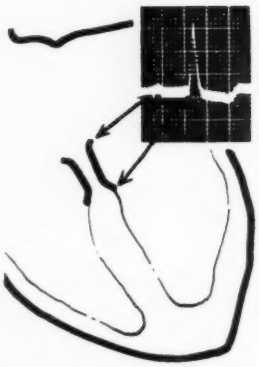
1. Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959. 2. David, N. A.; Logan, N. D., and Porter, G. A.: Evaluation of Thioridazine (Mellaril), a New Phenothiazine, in The Hospitalized Patient, A.M. & C.T. 7:364 (June) 1960.

ORIGINAL RESEARCH SERVING THE PHYSICIAN

SANDOZ



As a non-cardiologist do you understand the significance of the difference between these two tracings?



Interpretations of these and over 100 other tracings can be found in this new atlas type guidebook

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THE CARDIAC ARRHYTHMIAS

A Guide for the General Practitioner

This new book is written to help physicians who are not cardiologists to diagnose and treat cardiac arrhythmias through electrocardiographic interpretation. In a simple "picture and caption" style, Brendan Phibbs, M.D., helps you to develop an understanding of the differences between functional and pathological arrhythmias. The author uses a few concise well chosen words and nearly 150 large anatomic drawings and electrocardiograms like the ones above which show how disease of the atrioventricular node may extend the normal time of conduction. You'll find useful test problems in the back of the book to help you develop your skills further in using the electrocardiogram in the diagnosis of cardiac arrhythmias.

By BRENDAN PHIBBS, M.D., Casper Clinic, Casper, Wyoming. Ready later this month. Approx. 128 pages, 6¾" x 9¾", 144 cuts. About $6.75.

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3207 Washington Boulevard, St. Louis 3, Missouri

► ATLAS OF OBSTETRIC TECHNIC

By J. Robert Willson, M.D., Professor of Obstetrics and Gynecology, Temple University School of Medicine, Philadelphia. 304 pages with 55 plates. 1961, The C. V. Mosby Company, St. Louis. $14.50.

Presenting modern obstetric technic in pictorial form with a short explanatory text, this atlas also covers complicated obstetrics and lists the accepted procedures, including those in preoperative and in postoperative management. Since the text assumes the reader's basic knowledge of pelvic anatomy and obstetric physiology, it will be of greatest value to those whose skills have already been directed in this pursuit. It will best serve those who wish to modernize their obstetric technic quickly when faced with a complicated condition requiring surgery.

E. A. B.

► INTERNAL MEDICINE
A Physiologic and Clinical Approach to Disease

By Robert P. McCombs, M.D., Professor of Graduate Medicine, Tufts University School of Medicine, Boston. Ed. 2. 750 pages, illustrated. 1960, The Year Book Publishers, Inc., Chicago. $10.50.

The present edition of this book, as was the first, is divided into sections dealing with diseases of the heart, vascular system, kidneys, endocrine glands, lungs, gastrointestinal tract, blood, bones and joints; body fluids and electrolytes; infectious diseases; allergy; and nutritional and metabolic disorders. The new edition is longer than the first, and many changes and additions have been made to bring it up to date.

Since the text is relatively short, many of the subjects are covered in a brief fashion, and in many instances the bibliography is too incomplete to enable the reader to inquire further without consulting other sources of reference. Nonetheless, this book is an excellent introduction to the field of internal medicine.

R. V. R.

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Listings of books received are on pages 504 and 512.

now...prolonged antipruritic action in a pleasant-tasting chewable tablet

tacaryl T.M.

chewable tablets

METHDILAZINE, MEAD JOHNSON

prolonged antipruritic/antiallergic action...
not dependent on delayed intestinal release

Itching in children can now be controlled on b.i.d. dosage with a long-acting[1] antipruritic/antiallergic chewable tablet your pediatric patients will enjoy taking.

Tacaryl Hydrochloride is exceptionally valuable in alleviating many types of allergic and non-allergic pruritus. For example, in a group of children, 2 to 12 years of age, with atopic dermatitis, chickenpox, or contact dermatitis, 80 per cent obtained substantial or complete relief of their itching when treated with Tacaryl Hydrochloride. "No patient in this age group failed to show some degree of improvement."[2]

Tacaryl Hydrochloride is also effective in controlling symptoms in a wide variety of allergic conditions,[2-8] including hay fever and perennial rhinitis.

dosage: One Chewable Tablet (3.6 mg) twice daily. Adjustment of dose or interval may be desirable for some patients.

contraindications: There are no known contraindications.

side effects: Drowsiness has been observed in a small percentage of patients. Dizziness, nausea, headache, and dryness of mucous membranes have been reported infrequently.

cautions: If drowsiness occurs after administration of Tacaryl Chewable Tablets or Tacaryl Hydrochloride, the patient should not drive a motor vehicle or operate dangerous machinery. Since Tacaryl Chewable Tablets or Tacaryl Hydrochloride may display potentiating properties, it should be used with caution for patients receiving alcohol, analgesics or sedatives (particularly barbiturates). Because of reports that phenothiazine derivatives occasionally cause side reactions such as agranulocytosis, jaundice and orthostatic hypotension, the physician should be alert to their possible occurrence...though no such reactions have been observed with Tacaryl Chewable Tablets or Tacaryl Hydrochloride.

supplied: Pink tablets, 3.6 mg., bottles of 100.

references: (1) Lish, P. M.; Albert, J. R.; Peters, E. L., and Allen, L. E.: Arch. internat. pharmacodyn. *129*:77-107 (Dec.) 1960. (2) Howell, C. M., Jr.: North Carolina M. J. *21*:194-195 (May) 1960. (3) Clinical Research Division, Mead Johnson & Company. (4) Wahner, H. W., and Peters, G. A.: Proc. Staff Meet. Mayo Clin. *35*:161-169 (March 30) 1960. (5) Crepea, S. B.: J. Allergy *31*:283-285 (May-June) 1960. (6) Crawford, L. V., and Grogan, F. T.: J. Tennessee M. A. *53*:307-310 (July) 1960. (7) Spoto, A. P., Jr., and Sieker, H. O.: Ann. Allergy *18*:761-764 (July) 1960. (8) Arbesman, C. E., and Ehrenreich, R.: New York J. Med. *61*:219-229 (Jan. 15) 1961.

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Symbol of service in medicine

MARCH, 61 346R61

DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Mar. 1—To the airport in Madrid and on to Lisbon and to Porto Santo. At this barren island, we traveled in a faltering bus to the village square, where we waited for a boat to Madeira. The trip required four and one-half hours on a stormy sea. So late at night in Madeira and to beautiful Reid's Hotel, which overlooks the bay.

Mar. 2—To visit Marghab, where the finest embroidery in the world is made; then to the home of the Blandys with 800 acres of gorgeous gardens. After an evening visit to the antique shops, dined pleasantly in the hotel, and then to bed, reading "The Bachelor," by Muriel Clark.

Mar. 3—To walk among the shops and in the afternoon to drive far out on the island, viewing the great terraces planted with vegetables and the tremendous acreage of bananas. Rested on our piazza and read "Beyond Desire," by Pierre La Mure, dealing with the life of the composer Mendelssohn.

Mar. 4—Still in Madeira and today drove out to the village of Curral in the middle of the island.

Mar. 5—Early to the boat, which again required almost five hours from Funchal to Porto Santo, and after lunch by plane to Lisbon. Here to dine at the home of Dr. Almeida e Sa, and we talked of plans for the advancement of physical therapy and rehabilitation.

Mar. 6—At my desk in the Hotel Ritz in Lisbon dictating material for the periodicals. After luncheon, to visit the palace of the *Marqueza* de Fronteira, which has a library containing the music of all the great composers, including original drafts of their music and a collection of early histories and other publications of the sixteenth and seventeenth centuries. In the evening with *Senhora* Almeida e Sa and her family from the country to dinner at the Folclore.

Mar. 7—At noon came the Almeida e Sas for lunch and with them to view the great defense fortress on the banks of the Tagus River. Then to see the magnificent sculpture erected as a tribute to the great voyagers of Lisbon, and after that to see the Gulbenkian collection of art.

Mar. 8—By Pan American to New York and to the Waldorf to rest and to call the family.

Mar. 9—For breakfast came Bill White, Max Geffen and Peter Warren. Then with Charles Haney to drive to Peekskill, New York, and with Mrs. Margaret Donnelly to tour the hospital, finding it obsolescent yet marvelously conducted under the difficult conditions. In the evening some 600 attended a great dinner, and Dr. Frederick Rauch told of the hospital's needs. Dr. Burke, director of hospital planning for the State of New York, told of the contribution which the Hill-Burton funds would make, and old Pepys spoke of what would be required to bring the hospital with its modern new construction into an acceptable condition.

By plane to Washington, D. C. and to sleep at the Marriott Motel adjacent to the airport.

Mar. 10—In the morning driving through historical Virginia to Winchester to speak of current events in American medicine to the staff of the Winchester Memorial Hospital, with Dr. John C. Hortenstine presiding. Next to make a tape recording for promotions and to rest briefly before the banquet which 1000 attended. Dr. William P. McGuire, son of the great Dr. Hunter McGuire, presided at the dinner. Drs. John B. McKee, George H. Murphy, Jesse Clore and C. L. Riley and Dr. William G. Sanger, for many years head of the Medical College of Virginia, all spoke of the hospital's needs. State Senator Harry F. Byrd, Jr. presided and old Pepys spoke for an hour.

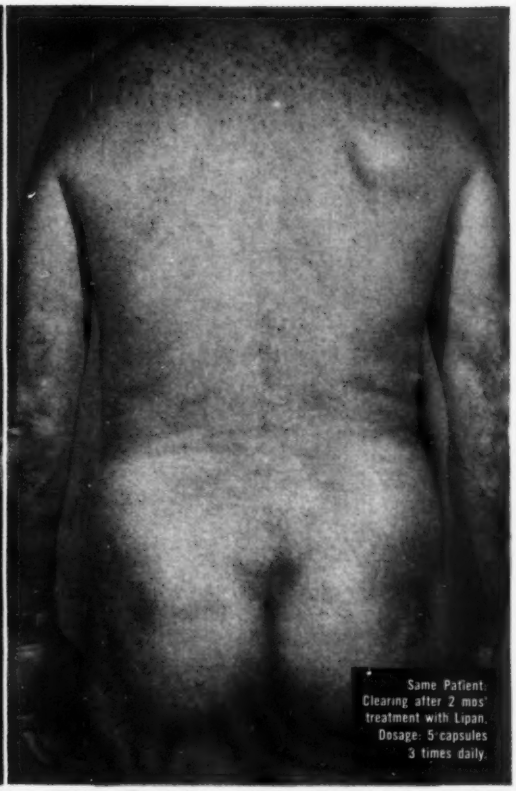
Mar. 11—To Mrs. Clapham's bookstore to sign my books and talk to those who came, and then returning to New York. In the evening with Mark and Rose Soroko to see a deep and philosophical play, "The Devil's Advocate," by Dore Schary, based on the novel by Morris L. West.

Mar. 12—To Rockefeller Hospital, where Tom Rivers lies ill, and we talked with him and Terese for some hours. Thereafter to dine at Lindy's.

Mar. 13—To my rooms came Drs. Hilleboe, Gitlin of the Children's Medical Center in Boston, Hodes of Mt. Sinai, New York, and Stokes of Philadelphia to rehearse for a panel on pediatric

(Continued on page A-152)

Psoriasis of 37 yrs' duration. Previous therapy produced no improvements.



Same Patient. Clearing after 2 mos' treatment with Lipan. Dosage: 5 capsules 3 times daily.

ACHIEVE FREEDOM FROM PSORIASIS W/LIPAN

Over and over again, studies have shown Lipan Improved Capsules to be orally effective therapy. Lipan will, in most cases, give a rapid clinical response. Maintenance dosage frequently keeps the patient symptom-free.

Again, in a recent study[1] on psoriatics of long standing, 37.71% showed complete remission of symptoms, 32.26% showed decided improvement, and 12.90% showed moderate or temporary improvement.

These new studies on the use of Lipan Improved Capsules have demonstrated that the clinical results are in direct proportion to adequate daily dosage.[2,3]

Effectiveness of Lipan therapy increases as dosage is increased.

Dosage: For complete *Lipanization* (saturation dosage): 2 to 4 capsules before each meal: 1 to 2 capsules before between-meal snacks.

Each Lipan Improved Capsule contains: Pancreatin – 2000 mg., Pyridoxine HCl – 3 mg.

Reprints, Samples and Literature upon request

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Waterbury, Conn.

REFERENCES: 1. Schwartzschild, L.: Oral Management of Psoriasis with a Lipotropic Agent. Clin. Med., Vol. 8, No. 4, (April) 1961.
2. Combes, F. C.: Management of Psoriasis as a Metabolic Lipid Disturbance. N. Y. St. Jrl. Med., Vol. 54, No. 13, July 1, 1954.
3. Rosenthal, T.: Management of Psoriasis. Clin. Med., Vol. 7, No. 3, (March) 1960.

PDR
PAGE 747

immunology. Thereafter all to lunch at the Waldorfkeller and then to record the panel. Later to dine with Sylvia and Milton Lasdon at the Marco Polo Club and to see a hilarious musical called "Do Re Mi."

Mar. 14—To the opening meeting of the National Health Forum, and saw George Armstrong, Bill Bauer, Ruth Freeman, Leona Baumgartner and many others concerned with public health. Dr. Baumgartner's address was particularly witty and full of challenge. At noon with Harold Diehl to lunch and to discuss new projects in education on cancer and in medical writing. Next to visit Herbert Mayes at the office of *McCall's*. Thereafter to the office of *Medical World News* and viewed the offices of Bill White, discussing problems of editing and publishing. Later came Louis L. Tyrrell of Teletalent, Inc., to speak of new methods of education using sound motion pictures in individual sets.

Mar. 15—Participants came early for "The Voice of Medicine" panel on mental retardation, including Dr. Alan Guttmacher of New York's Mt. Sinai Hospital, Dr. Arthur Parmelee of Los Angeles, Drs. Sherman Kaplitz and Meyer Perlstein of Chicago, and Dr. Theodore Kushnick. Thereafter all to lunch, and then to the plane for Chicago, reading en route Henry Roth's novel, "Go With Sleep."

Mar. 17—To Don McNeill's Breakfast Club; then back to the desk and soon came Messrs. Mann and Nederlander of Detroit to discuss a new project in diagnosis and recreation. Thereafter to the Congress Hotel, where Albert Pick entertained the board of La Rabida.

MY INSTITUTE

With bursting pride I saw
my monster rise—
My Institute, whose girders
scrape the skies.
The hammer and the shattering
drill to me
Were like the quires of
angels' minstrelsy.
Finished at last! The
final painter's mate
Went down the lift and clanged
its brassy gate.
In clouds of straw we now
unpack the gear;
Machines with splendid knobs
and dials appear,
Machines which type the answers
and, it's said,
Will write your thesis while
you snore in bed.
And now, white-coated, my
assistants stand,
With fair technicians all at
my command.
Already foreign visitors with smiles
Beg reprints from our vast
enameled files.
I stand there dumb. The
visitors are waiting.
I can't remember what we
are investigating!

From the Lancet

* * *

Mar. 18—Today came Lothar Ragoczy from Copenhagen, who has been heading the Danish Foundation for Infantile Paralysis with great success for many years, and with him his charming lady. We showed them our great city, and in the evening dined with John Sheinin, Neison Harris and others of the Chicago Medical School.

Mar. 19—In the morning showed our guests the north side of the city and the County Medical Center, and then for luncheon at the Pump Room. Thereafter to the Museum of Science and Industry and the University of Chicago. Next to the Art Institute, and in the evening to the Guildhall of the Ambassador West, where the Julian D. Levinson Foundation for the Mentally Retarded held its annual meeting. Mrs. Herman Jacobson presided with her accustomed skill, and here also were Dan Ryan, Sam Hoffman, Fred Hertwig and other notables, and old Pepys spoke of the need for research in this area.

Mar. 20—To luncheon came the Ragoczys and then for a conference with Mr. Arstark of the Parkinson Foundation.

Mar. 21—This day had conferences with representatives of the Cancer Prevention Center and the Weizmann Institute of Israel. Later came Mascularis of Greece to confer on abstracting.

Mar. 22—To the station to greet Dr. and Mrs. Hugh Clegg of London—he being editor of the *British Medical Journal*—en route homeward from the meeting of the British Medical Association in New Zealand. In the evening to the annual meeting of the Hektoen Institute for Medical Research of the Cook County Hospital.

Mar. 23—In the evening Dr. and Mrs. Blasingame entertained at the University Club for Dr. and Mrs. Clegg, and there met again Tommie Hendricks, Frank Hammond, John Talbott, John Youmans and all the ladies.

Mar. 24—At noon with the Cleggs to luncheon, where Major Lohr of the Museum of Science and Industry presided, and the guests included officers of the Fifth Army. In the evening to visit the Hall of Fame of the International College of Surgeons.

Mar. 25—At noon came many of our friends, associates and medical leaders to attend a luncheon honoring the Cleggs. Among them were the deans—the two

(Continued on page A-154)

NEW INHIBITOR OF GASTRIC ACID SECRETION

NACTON®

poldine methylsulfate

in PEPTIC ULCER/HYPERCHLORHYDRIA

- suppresses gastric acid secretion at the parietal cell level
- decreases gastrointestinal spasm and hypermotility

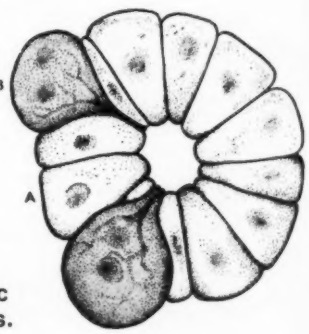
NACTON®... Has been shown to suppress gastric acid secretion for as long as 8 to 9 hours.[1] "...reduces the total output of gastric HCl by about 60%."[2]

Decreases hypermotility of stomach and bowel.[3-7]

Aids healing of peptic ulcer.[8]

Unusually low incidence of side effects.[1, 3, 9]

NACTON TABLETS...4 mg.
Average effective dose:
4 mg. three or four times daily



Typical gastric secretory gland.
A—chief cell (pepsin-producing).
B—parietal cell (acid-producing).
NACTON effectively inhibits gastric acid production by the parietal cells.

References:
1. Douthwaite, A. H., and Hunt, J. N.: Effect of "Nacton" in Patients with Duodenal Ulcer, Brit. Med.J. *1*:1030-1034 (May 3) 1958. 2. Douthwaite, A. H.: The Development of the Treatment of Duodenal Ulcer, Proc. Roy. Soc. Med. *51*:1063-1068 (Dec.) 1958. 3. Steigmann, F.: The Problems of Side Effects in Anticholinergic Therapy, to be published. 4. Grossman, M. I., and Tuttle, S. G.: Clinical Report to McNeil Laboratories. 5. Texter, E. C.: Clinical Report to McNeil Laboratories. 6. Cayer, D., and co-workers: Clinical Report to McNeil Laboratories. 7. Lorber, S. H.: Clinical Report to McNeil Laboratories. 8. Walker, G. F.: Therapeutics; Gastric Sedatives, Brit. J. Clin. Pract. *13*:382 (May) 1959. 9. Douthwaite, A. H., Hunt, J. N., and MacDonald, I.: A Long-Acting Inhibitor of Gastric Secretion, Brit. Med. J. *2*:275-276 (Aug. 3) 1957.

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Bennetts and Sheehan; Hesseltine from the Illinois State Medical Society; Van Dellen from the Chicago Medical Society; Hoffman from Hektoen Institute; Darley from the Association of American Medical Colleges; Talbott, editor of the *Journal of the American Medical Association*; Bay, Adams and Palmer from the University of Chicago; Turner from the International College of Surgeons, and the writers Kleckner and Effie Alley.

This evening with the Cleggs to the annual dinner-dance of the Jackson Park Branch of the Chicago Medical Society, where Dr. Joseph Kirsner presided and Clegg told of his travels and of the difference between nations in the practice of medicine.

Mar. 26—For a walk with Clegg around the University of Chicago, and later to a great reception at the Italian consul's.

Mar. 27—Hugh Clegg visits the headquarters of the American Medical Association. In the afternoon to a tea in the headquarters of the Chicago Heart Association, where came also Emmett Bay, Walter Priest with his two sons, Aldo Luisada, and others concerned with the book "Heart Care." Thereafter to the home of John Talbott, where came also the Blasingames.

Mar. 28—This day the Cleggs departed for Philadelphia. In the evening old Pepys went to the University of Chicago to dine with Nu Sigma Nu and to give the Ernest E. Irons lecture. Here Mark Cooper presided, Dr. Palmer spoke of the work of Ernest Irons, and Dean Ceithaml graced the occasion.

Mar. 29—At noon to the Chicago Heart Association, where Mark Lepper presided, for the report of all the agencies and committees dealing with public health education. Next to meet with the podiatrists, who plan a new hospital for the medical center.

Mar. 30—By early plane to Memphis, giving interviews to the *Press-Scimitar* and then dining with the bankers in the directors' room of the Union Planters Bank. Here were Parsons, Thurston Asherson and Kinney. In the evening to the Executives Club, and saw here many friends, including McDaniel of Tyronza, Arkansas; Hyman, dean of the medical school, and Graves, the health officer. And old Pepys gave a talk on the progress of medicine.

Mar. 31—Returned by plane and in the evening to dine with the Friedells, inaugurating the beginning of the Passover.

The Medical Muse

RICHARD ARMOUR

FAT CHANCE

There is a possibility that obesity is caused by a disorder of the hypothalamus.—*News item.*

Let's say you have a patient who
Eats more than anyone, or two,
And of the many things she eats
Most loves to gorge on starches, sweets.

Now you could tell her she is lacking
In self-control, and have my backing,
Or make her switch, if all else fails,
To biting on her fingernails.

Or you could say, "Now don't you fuss,
It's naughty hypothalamus,
No fault of yours." She'd love you dearly,
And get to weigh a ton, or nearly.

HIGH RATIO

Among the greater metropolitan areas with populations of a million or over, the Boston area has the highest ratio of physicians to population.—*News item.*

Why is it doctors are the thickest
In Boston? Are the people sickest?
If so, and this is rather odd,
Is it from eating beans and cod?

Or do the doctors swarm in legions
Around the proper Back Bay regions
Because they find it elevated
To treat the Harvard educated?

We do not know the reason, but
To young M.D.'s who know what's what
We'd say: Seek out, sir, some metropolis
Where doctors are not quite so popolis.